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THE PHYSIOLOGY OF DIGESTION.

MERCERS' COMPANY LECTURES

ON

RECENT ADVANCES

IN THE

PHYSIOLOGY OF DIGESTION

DELIVERED IN THE MICHAELMAS TERM, 1905, IN THE PHYSIOLOGICAL DEPARTMENT OF UNIVERSITY COLLEGE, LONDON.

BY

ERNEST H. STARLING, M.D., F.R.S.,

JODRELL PROFESSOR OF PHYSIOLOGY.

WITH TWELVE ILLUSTRATIONS.

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PREFACE.

In recognition of a generous gift by the Mercers' Company in aid of the work of the Physiological Department at University College, the Council of the College resolved that a course of Lectures should be given each year dealing with the original investigations made in the Department.

In presenting this first course of Mercers' Company Lectures I have attempted, in the light of researches which have been carried out in this laboratory, to give an appreciation of the present state of our knowledge on certain aspects of the subject of digestion, in preference to describing at length the researches themselves, which can be read in the original papers enumerated at the end of this book.

The great development in this branch of Physiology, which has taken place in recent years, owes its inception to the masterly series of researches carried out by Pawlow in the Institute of Experimental Medicine at St. Petersburg, researches to which I shall have repeated occasion to refer in the course of the following Lectures. Two other important lines of investigation have presented themselves as necessary to the proper understanding of the biological facts elucidated by Pawlow. The first of these is the study of the chemical and physical conditions which determine the digestive changes in the food-stuffs. As will be seen in the first two Lectures, we approach here a subject which must play a great part in all our future conceptions of intracellular mechanism, *i.e.*, the study

of chemical and physical changes in capillary and colloidal systems, where the modification of physical condition occurring at surfaces determines changes of quite another order to those which have so far formed the chief pre-occupation of physics and chemistry.

The second line had its starting point in the discovery that the pancreas is normally excited to secrete, in response to stimuli originating in the gut, not, as Pawlow thought, by means of the nervous system, but by the dispatch of a chemical messenger or hormone from the seat of stimulation to the reacting gland through the blood-stream. Subsequent investigations have shown the existence of other chemical correlations of the same nature and suggest that, by the detection and isolation of such hormones, we may later be in a position to influence and control a number of the chief functions of the body.

I trust that the publication of these Lectures may serve to interest a larger audience of students and medical men in the "growing border" of these important subjects and to give them some idea of the aims and objects of this branch of physiological research.

ERNEST H. STARLING.

Physiological Laboratory,
University College,
March, 1906.

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THE PHYSIOLOGY OF DIGESTION.

LECTURE I.

THE FOOD-STUFFS AND THEIR CHANGES DURING DIGESTION—THE MODE OF ACTION OF FERMENTS.

Physiology deals with the sources and the transformations of energy in the living organism. In animals the whole of the energy available for the vital processes is obtained by the combustion of the food-stuffs, *i.e.*, the union of their carbon and hydrogen with the oxygen taken in from the surrounding atmosphere. The office of digestion being to prepare the food-stuffs for absorption into the fluids of the body and for utilisation by its constituent cells, the chapter in physiology dealing with this subject logically precedes all others. In the following lectures I propose to deal with the changes undergone by the food in the alimentary canal, and especially with the mechanisms by which these changes are brought about. The time at our command will not allow me to enter into full details in every part of the subject; I shall therefore devote my chief attention to those questions which are at present being most actively discussed by physiologists, and to the solution of which I am able to bring the experience of work which has been carried out in this laboratory.

In the bewildering variety of foods that are at the disposal of civilised man, it would seem at first sight hopeless to attempt

to give a description of the principles which underlie the digestion of each one of them. A chemical examination of these food-stuffs, however, reveals the possibility of a very simple classification. All the foods which serve to us as sources of energy are themselves derived from living beings, either plant or animal. The chemistry of the food-stuffs is, therefore, identical with the chemistry of the tissues of living organisms. The substances which are utilised in the building up of a plant or animal fall into one of three main groups, which are also the groups into which our food-stuffs are divided. These groups are—

(1) Proteids—nitrogenous bodies such as those forming the greater part of meat or white of egg. These can be split up readily by hydrolytic agencies into a whole series of mono-amino- and diamino- acids, derived chiefly from the fatty series but partly also from the aromatic series. They also contain sulphur as an integral part of their molecule, chiefly in the form of cystin, which itself is derived from two amino-acid groups.

(2) Carbohydrates, including the starches and sugars.

(3) Fats, which are compounds of glycerin with fatty acids.

I have spoken of these foods as sources of energy to the body. Is this their sole significance? The energy value of food is easily determined by finding how much energy in the form of heat a given weight of it will evolve when burned in an atmosphere of oxygen. In this way we might find the following heat equivalents for the three classes of food-stuffs, namely—

Proteids	5·5	kilocalories.
Carbohydrates	4·1	,,
Fats	9·5	,,

One gramme of fats, for instance, when burned in an atmosphere of oxygen to CO_2 and H_2O, will evolve an amount of heat which is sufficient to warm 9·5 kilogrammes of water from 0°C.

to 1°C. If the energy value of a food-stuff represents its whole value to the organism, we should expect that the animal would be able to nourish itself and discharge its normal activities at the expense of any one of these food-stuffs, provided that this were given in proportion to its energy or heat value. Within limits this is the case. If an animal be made to do more work, or be exposed to external cold, so that it needs more heat to maintain its normal temperature, the amount of food which it takes must also be increased, and it seems to be a matter of indifference to the organism which class of food-stuffs is used to furnish this excess. From the energy point of view the value of a food is the amount of heat which it will evolve when burned to CO_2 and H_2O. From this point of view the nitrogen in the proteid molecule is practically valueless, and it is only the C and H atoms in the proteid which can be regarded as furnishing energy to the body. If an animal be compelled to satisfy a large call on its energies by taking increased proteid food, the useless nitrogen in the molecule, which is set free by the utilisation and combustion of the carbon and hydrogen, must be discharged from the body, and as a matter of fact we find that, with increased proteid diet, there is corresponding increase in the output of nitrogen in the form of urea. As a source of energy, proteid cannot be regarded as presenting any advantages over carbohydrate and fat. In fact, it suffers from the disadvantage that, for the utilisation of its energy, nitrogen has to be split off, probably in the form of ammonia, and a certain amount of useless work has to be done in the transformation of this nitrogen into urea and its excretion from the body. Although, however, the nitrogen in the food is useless as a source of energy, its presence is an essential condition for the utilisation of the energy of the other food-stuffs, and it must be regarded, therefore, as one of the most important constituents of all living organisms. In fact, the protoplasm,

the active part of the organism, consists almost entirely of proteids or allied bodies. Fats and carbohydrates, where they occur in the living organism, are found only to a slight extent in combination in the living protoplasm itself, the greater part of them being laid down as store material for the future wants of the active growing protoplasm. Many facts show that the combustion and utilisation of the energy of the carbon and hydrogen of the food take place in the protoplasm itself, the oxidisable molecules being linked on to the central living nucleus; and it seems that nitrogen plays an important part both in this linkage, and in bestowing on the complex thus produced the lability or instability which is a necessary condition of the vital processes themselves.

Essential functions of all living beings are those of growth, repair, and in the higher animals death. No act can go on without involving some degree of disintegration of the living nitrogenous framework of the tissue, and the consequent need of repair. In every living cell, therefore, we may speak of two kinds of chemical changes, or of two destinations of the food-stuffs. In the first place there are the changes which furnish the energy necessary for vital manifestations, movement, warmth, etc. As sources of this energy, all three classes of food-stuffs can be employed, their value being given by their heat equivalents when taken as food. In the second place we have the changes which are involved in the disintegration, repair, and growth of the living protoplasm itself. In this nutritional metabolism proteids play the most important part, and are absolutely essential for the continuance of life. An animal, therefore, can theoretically be nourished on a diet of pure proteid, but it would be impossible to keep an animal alive on a diet consisting either of pure fat or of pure carbohydrate.

These three classes of food-stuffs being essential constituents of all our foods, the use of the processes of digestion is to

render them fit for absorption into the blood, by which they may be carried round to all parts of the body. In most cases they cannot be utilised in their original form by the living cells. It must be remembered that, when we nourish ourselves at the expense of an animal or plant, we are taking in, not only the current coin of the organism which is being used for the supply of energy to its vital processes, but also, and to a much larger extent, the framework forming the machinery of the organism, as well as its stores of carbohydrate or fat. The food-stuffs therefore as we ingest them are in the most inactive form possible. Practically all of them are colloidal, free from taste or chemical reaction, and presenting no tendency to unite with oxygen, or indeed to undergo any change whatsoever, apart from the interference of living organisms such as bacteria. In a starving animal, the stores of carbohydrate and fat and the proteid structure of the living cells have to be converted into a soluble form, transformed, so to speak, into currency, before they can be utilised by other living cells for the discharge of their normal functions and the maintenance of the life of the animal. In the same way, when we take these colloidal or insoluble stable substances into our alimentary canal, they have to be dissolved and rendered diffusible, in order to allow of their easy transference across the wall of the gut into the blood and their transport to the tissue cells. On fats and carbohydrates, therefore, the effect of digestion will be to render them soluble and diffusible, and to reduce them to a condition in which they can be directly assimilated by the cells of the body. These latter cannot deal, for example, with all kinds of carbohydrate. Many an animal cell will starve when presented with starch, dextrin, or any of the disaccharides, such as maltose, lactose, or cane sugar. It is necessary, therefore, that all the carbohydrates shall be

reduced in the alimentary canal or in its walls to the form of monosaccharides. As regards proteids, the processes of digestion have a different significance according as we are dealing with their value as givers of energy or their value as builders up of the living protoplasm. If the proteids of the food are to be oxidised and utilised as a source of energy, it is only necessary to render them soluble so as to assist their absorption. If, however, they are to be built up as integral parts of the living cells, to take the place of molecules which have been destroyed in the wear and tear of the processes of life, a much more profound change is necessary. The proteids of the cells from different parts of the body have different molecular constitutions. Not only do they differ among themselves, but they differ very largely from many of the proteids which may be taken in with the food. A child is able to obtain material for the growth of his brain cells, his muscle cells, his liver cells, from a diet containing proteid in the form of caseinogen, of vegetable gluten, of meat fibrin, or vegetable proteid, such as edestin. A reference to the following tables will show the striking difference in composition between the various proteids of the food and the proteids which have to be formed from them in the living tissues.

We may take for example the manner in which the nitrogen is combined in the different proteids. For purposes of classification the nitrogen can be divided into three fractions, according to its behaviour in the product of the acid hydrolysis of the proteid. These fractions are—

(*a*) The portion which is driven off as ammonia by heating the acid mixture with alkalies or magnesia, the so-called ammonia- or amide-nitrogen;

(*b*) That contained in the form of monoamino-acids;

(*c*) That contained as diamino-acids, or as bases such as

guanidine, histidine, or arginine, etc., known as basic nitrogen and precipitated on addition of phosphotungstic acid.

In the following table* is given the relative distribution of the nitrogen in various proteids among these three groups:—

Proteid.	Amide N.	Basic N.	Monamino-N.
Crystallised serum albumin ..	6·5	34·4	60·2
Crystallised egg albumin ..	8·5	21·3	67·8
Crystallised edestin	10·2	38·1	55·0
Caseinogen of milk	10·4	28·9	62·0
Serum globulin	8·9	25·0	68·3

Still greater differences are noticeable when we examine the content in certain individual constituents of the proteid molecule, thus:—

Proteid.	Arginin.	Lysin.	Histidin.	Tyrosin.	Cystin.
Edestin	14·07	—	—	—	—
Caseinogen	4·84	5·80	2·59	4·5	—
Blood fibrin	—	—	—	3·82	1·17
Gluten fibrin (wheat) ..	3·05	—	1·53	—	—
Zein (maize)	1·82	—	0·81	—	—
Egg albumin	—	—	—	1·5	0·29
Serum albumin	—	—	—	2·0	2·15

It is evident that to form serum albumin, for instance, out of wheat gluten, an entire reconstruction is necessary. This can only be accomplished by taking the proteid molecule to

* From Hofmeister, "Ergebnisse der Physiologie," I., i. (1902), p. 777.

bits, and by selecting certain of its constituent parts and building these up in the proper proportions to form a new proteid molecule. For the purposes of nutrition the changes in the proteid molecule in the intestine must be profound, and the extent of the change must be greater the more variation there is in the composition of the proteid of the food from the composition of the proteids of the tissues.

In primitive alimentary canals, every cell lining the canal may be endowed with amœboid properties and capable of devouring food particles, the subsequent changes in the food particles to fit them for their journey through the rest of the body being performed in the body of the cell itself. In all the higher animals, however, including ourselves, the greater part of the preparation of the food is accomplished extracellularly in the lumen of the alimentary canal, and the changes are effected by means of special digestive juices, which are formed by the activity of masses of cells produced as outgrowths from the wall of the canal. The digestive juices attack the food-stuffs by means of ferments, and in every case the action of these ferments is hydrolytic, the food-stuffs taking up one or more molecules of water and undergoing dissociation into simpler molecules. Since each class of food-stuff requires a different ferment, a great variety of ferments are concerned in the processes of digestion. In the following list the ferments of the alimentary canal are enumerated, together with the substances on which they act and their ultimate products :—

Food-stuff.	Ferment.	Product of action.
Proteids (all)	Pepsin	Albumoses and peptones (amino-acids after prolonged action).
	Trypsin	Peptones, amino-acids and bases (complete hydrolysis).

Food-stuff.	Ferment.	Product of action.
Hydrated proteids and certain coagulable proteids such as fibrin and caseinogen	Erepsin	Amino-acids, etc.
Carbohydrates—		
Starch	Amylase of saliva ..	Dextrin and maltose.
	,, of pancreatic juice	
Maltose	Maltase	Glucose.
Cane sugar ..	Invertase	Glucose and fructose.
Milk sugar ..	Lactase . ..	Glucose and galactose.
Fats	Lipase (steapsin) ..	Fatty acids and glycerin.

It will be seen that, as the end result of digestion, the enormous variety of food taken by man is reduced into a fairly small number of simpler bodies. These end products are :—

(1) Carbohydrates.

The monosaccharides: glucose, fructose or lævulose, and galactose.

(2) Fats: fatty acids, or (in alkaline medium) soaps, and glycerin.

(3) Proteids. Here we have a great variety of mono- and diamino- acids, which may be enumerated as follows :—

MONOAMINO-ACIDS—	
Glycine (aminoacetic acid)	Monobasic acids of fatty series.
Alanine (aminopropionic acid)	
Serine or oxyalanine (oxyaminopropionic acid)	
Aminovalerianic acid	
Leucine (aminoisobutylacetic acid)	
Isoleucine (aminocaproic acid)	
Aspartic acid	Dibasic acids.
Glutamic acid	
Phenylalanine	Benzene (aromatic) derivatives.
Tyrosine (oxyphenylalanine)	
Proline (pyrrolidine carboxylic acid)	Heterocyclic compounds.
Oxyproline (oxypyrrolidine carboxylic acid) ..	
Tryptophane (indol-aminopropionic acid) ..	

Diamino-acids and their Compounds—	
Lysine (diaminocaproic acid)	The 'hexone bases.'
Arginine (guanidinaminovalerianic acid) ..	
Histidine (a pyrimidine derivative)	
Diaminotrioxydodecoic acid ..	derived from a 12 carbon acid.
Cystin (derived from aminothiolactic acid) ..	Sulphur-containing body.

The whole of these digestive changes in the food-stuffs are to be ascribed to the action of ferments. When, following the food through the walls of the intestine, we have to deal with the processes by which it is assimilated into the living cell, and the processes by which it undergoes oxidation or disintegration and so furnishes energy to the body, as well as the processes by which one cell may be nourished at the expense of other less important cells, in every case we find that ferments are involved. It is impossible, therefore, to proceed further with our study of the digestive juices, without trying to form some conception of the manner in which these bodies, the most important factors in the maintenance of life, effect their changes.

It is important to note that all the changes wrought by the digestive ferments on the food-stuffs are hydrolytic in character. Thus the proteids are transformed by the action of pepsin or trypsin into the hydrated proteids, albumoses or peptones, and these again by the further process of hydration into the amino-acids. Starches take up water with the formation of maltose. Each molecule of the disaccharides takes up one molecule of water, and is converted into two molecules of a monosaccharide. Each molecule of neutral fat takes up three molecules of water to be transformed into glycerin and the corresponding fatty acid. If the food-stuffs are placed in contact with water, either at ordinary temperatures or at the temperature of the body, and bacteria be excluded from the solution, they undergo practically no

change. If the solution be warmed, a slow process of hydration takes place, which is quickened by rise of temperature, so that in water heated above boiling point hydration occurs with considerable rapidity. We may say, then, that the action of the ferments is to quicken a process of hydrolysis which, without their presence, would take an infinity of time for its accomplishment. In this respect their action is similar to that of acids, and indeed of a whole class of bodies which are spoken of as catalysers or catalysts. A catalyser is a substance which will increase the velocity of a reaction without adding in any way to the energy changes involved in the reaction, or taking any part in the formation of the end products. Since the catalyser is unchanged in the chemical process which it brings about or hastens, a very small quantity is able to influence reactions involving large quantities of other substances. By adding acids to a watery solution of the food-stuffs, the process of hydrolysis is quickened in proportion to the strength and concentration of the acid. The effective catalytic agents in this process appear to be the hydrogenions of the free acid. There are many other substances besides the free acids, which may act as catalysers, and a study of the conditions under which catalysis takes place may throw some light on the essential nature of the action of ferments.

The velocity of almost any reaction in chemistry can be altered by the addition of some or other catalytic agent, and there are few of the ordinary reactions in which catalysis does not play some part. Among such processes we may instance the action of spongy platinum on hydrogen peroxide. Hydrogen peroxide undergoes slow spontaneous decomposition into water and oxygen. If, however, a little spongy platinum be added to it, it is at once seen to decompose rapidly with the evolution of bubbles of oxygen, and the action does not cease

until the whole of the hydrogen peroxide has been destroyed. Spongy platinum is able in the same way to quicken a very large number of chemical reactions. Thus sulphur dioxide and oxygen when heated together will combine very slowly; the combination becomes rapid if a mixture of the two gases be passed over heated platinum. The same reaction, namely the combination of sulphur dioxide with oxygen, may be quickened by the addition of a small trace of nitric oxide, and this fact is made use of in the manufacture of sulphuric acid on a commercial scale by the ordinary lead chamber process. Hydrogen peroxide and hydriodic acid slowly interact with the formation of water and iodine. This reaction may be quickened by the addition of many substances, among which we may mention molybdic acid.

It might be thought, however, that, although there is this superficial resemblance between the action of catalysers and that of ferments, certain important characteristics of the ferments might serve to make a wide cleavage between the two processes. Thus among the ferments we find a marked specificity. We may take as examples the ferments which act on the disaccharides. Any of the disaccharides, whether natural or artificial, can be readily converted by treatment with acids into the corresponding monosaccharides. Thus cane sugar treated in this way gives equal parts of fructose and glucose. Lactose will give equal parts of glucose and galactose. Maltose is entirely transformed into glucose. When we come to the ferments, however, we find that invertase, which quickly transforms cane sugar into fructose and glucose, has not the slightest action on either of the other disaccharides. In order to split up lactose we have to make use of a special ferment, lactase; and similarly for the conversion of maltose into glucose we must employ the ferment maltase. The action of these ferments is not, however, so

specific as would appear when we confine our attention to the food-stuffs themselves. Thus invertase not only breaks up cane sugar, but also causes hydrolysis of raffinose and gentianose. Lactase, in addition to its action on lactose, or milk-sugar, has the property of hydrolysing all the β-galactosides. Emulsin hydrolyses the β-glucosides (*i.e.*, most of the natural glucosides), as well as the β-galactosides, including milk-sugar. Maltase not only converts maltose into glucose, but also hydrolyses all the α-glucosides. On the other hand, although some substances such as platinum, especially in the finely divided form of platinum black, can influence a very large number of reactions, they cannot influence all chemical reactions. Potassium bichromate will act as the catalyser for the oxidation of hydriodic acid by bromic acid, but not for the oxidation of the same substance by iodic acid. Iron and copper salts in minute traces will quicken the oxidation of potassium iodide by potassium persulphate, but have no influence on the course of the oxidation of sulphur dioxide by potassium persulphate. Tungstic acid increases the velocity of oxidation of hydriodic acid by hydrogen peroxide, but has no effect on the velocity of oxidation of hydriodic acid by bromic acid, and these examples may be multiplied to any extent. One cannot therefore regard the limitation of action of the ferments as justifying any fundamental distinction being drawn between the action of this class of substances and that of catalysts.

Another contrast has been drawn between the effects of rise of temperature on these two classes of phenomena. Whereas the influence of most catalysers on the velocity of a reaction increases rapidly with increase of temperature, in the case of ferments this increase occurs only up to a certain point. This point is spoken of as the optimum temperature of the ferment action. If the mixture be heated above this point the action of the ferment rapidly slows off and then ceases. This

contrast again is only apparent. The ferments are unstable bodies easily altered by change in their physical conditions, and destroyed in all cases at a temperature considerably below that of boiling water. We may say, therefore, that ferment actions, like catalytic actions, are quickened by rise of temperature, but this effect of temperature is finally put a stop to by the destruction of the ferment. The same effect of temperature is observed in the case of inorganic catalysers whose physical state is susceptible, like that of the ferments, to the action of heat. By the passage of electric sparks between two platinum terminals immersed in distilled water, minute ultra-microscopic particles of platinum are thrown off into the fluid, so that a *colloidal solution* of platinum is obtained. This colloidal platinum exerts marked catalytic effects on various reactions, *e.g.*, on the decomposition of hydrogen peroxide and on the combination of hydrogen and oxygen. The effect, however, presents an optimum temperature, owing to the fact that the colloidal platinum is altered, coagulated, and thrown out of solution when this is heated to near boiling point. We may therefore employ either class of reactions in trying to form some conception of the processes which are actually involved.

Very many theories have been put forward to account for this action of catalysers or of ferments. Many of them are merely transcriptions in words of the processes which actually occur, and fail to throw any light on their real nature. The essential phenomena involved fall directly into two classes. In the first place, it must be remembered that the molecules of any liquid or gas, which are situated in the surface layer in contact with some other substance, are in a different condition from those in the interior of the fluid. In gases this difference results in a diminution of the pressure or of the translatory velocity of the molecules in the surface,

and therefore to a condensation of the gas here. After a glass vessel has been evacuated by means of a mercury pump, it is found that the vacuum slowly diminishes, owing to the gradual giving off by the glass of the so-called occluded gas, *i.e.*, gas which has been adherent to its surface, and perhaps in actual solution in its superficial layers. The glass gives up this occluded gas very slowly, and in order to make a perfect vacuum the process of evacuation has to be repeated several times, and the glass must be heated considerably during the operation. In many cases the combination of gases can be hastened by increasing the surface to which they are exposed, as by passing them over broken porcelain or powdered charcoal. The power of a solid to condense gases on its surface varies with the nature of the solid and the nature of the gas. It is very marked in animal charcoal, especially in the case of gases such as ammonia or sulphur dioxide. Metals also have some power of occluding or condensing at their surfaces. Thus both platinum and palladium will absorb a very large amount of hydrogen. In the same way silver has the power of occluding oxygen. That this effect is a surface phenomenon is shown by the fact that the power of these metals or substances to occlude gases is in proportion to their state of subdivision. The same proportionality holds between the surface of these substances and their catalytic power. Thus the efficacy of platinum in hastening the combination of hydrogen and oxygen is in direct proportion to its fineness of subdivision, and is best marked when the metal is reduced to ultra-microscopic dimensions, as in the colloidal solution of platinum. Every colloidal solution must be regarded as presenting an enormous surface in proportion to the mass of substance in solution. Thus a sphere of 10 cubic centimetres with a surface of 22 square centimetres, if reduced to a fine powder consisting of spherules about 0·00000025 cm.

in diameter, will have a surface of 20,000,000 square centimetres, *i.e.*, nearly half an acre.*

There is a direct proportionality, therefore, between the power of a substance to condense a gas on its surface and its power to quicken the velocity of chemical changes in which the gas is involved. The same process of condensation occurs with dissolved substances. Just as the pressure of a gas in immediate contact with a solid body is diminished, so the osmotic pressure of a substance in solution is diminished at the surface. Hence there is a diffusion of dissolved substances towards the region of lower osmotic pressure *i.e.*, a concentration of dissolved substances at the surface of contact. It was suggested by Faraday that the catalytic property of surfaces was due to this condensation of molecules, and the consequent bringing of the two sets of molecules within each other's sphere of influence. Whether this is the sole factor involved is doubtful, since mere compression of gases or increased concentration of solutions does not in the majority of cases result in such a quickening of the velocity of reaction as is brought about by the effect of the surface.

It is possible that this condensation effect may in every case be combined with the second factor, which we must now consider, namely, the formation of intermediate products. If we take an alkaline solution of indigo, and boil it with some glucose, the indigo is reduced, giving up its oxygen to the glucose. The mixture therefore becomes colourless. On shaking with air, the colourless reduction product of the indigo absorbs oxygen from the atmosphere and is re-transformed into indigo. These two processes can be repeated until the whole of the glucose is oxidised, and the process can be made continuous if air or oxygen be bubbled through a hot

* V. Mellor's, "Chemical Statics and Dynamics" (Longman's, 1904), esp. pp. 245 *et seq.*

alkaline solution of glucose containing a small trace of indigo. In this case the indigo does not add to the energy of the reaction. It appears unchanged among the final products, and a small amount may be used to effect the change of an infinite quantity of glucose. It therefore may be said to act as a ferment or catalytic agent. Instead of an alkaline solution of indigo, we may use an ammoniacal solution of cupric oxide for the purpose of carrying oxygen from the atmosphere to the glucose. This is reduced to cuprous hydrate on heating with sugar, but cupric hydrate can be at once re-formed by shaking up the cuprous solution with air. It has been thought that a large number or all of the catalytic reactions occur in the same way by two stages, *i.e.*, by the formation of an intermediate product. Thus in the ordinary process for the manufacture of sulphuric acid the nitric oxide may be supposed to combine with the oxygen of the air to form nitrogen peroxide. This interacts with sulphur dioxide, giving sulphur trioxide and nitric oxide once more. The nitric oxide, which we alluded to before as the catalyser, may in this way be regarded as the carrier of oxygen from air to sulphur dioxide. It has been suggested that the action of spongy platinum or colloidal platinum rests on the same process, and that in the oxidation of hydrogen, for instance, PtO or PtO_2 is formed and at once reduced by the hydrogen with the formation of water.

There is a certain amount of experimental evidence in favour of this hypothesis. According to Engler and Wöhler,* platinum black, which has been exposed to oxygen, in virtue of the gas which it has occluded, has the power of turning potassium iodide and starch blue. This power is not destroyed by heating to 260° in an atmosphere of CO_2, or by washing with hot water. On exposure of the platinum black to hydrochloric acid, a certain amount is dissolved, and the substance loses its effect on potassium iodide. The amount dissolved corresponds with the amount

* Quoted by Mellor, *loc. cit.*, p. 269.

of iodine liberated from potassium iodide, and also with the amount of oxygen occluded, the (soluble) platinum and oxygen being in the proportions necessary to form the compound PtO.

But why should a reaction take place more quickly if it occurs in two stages instead of one? The formation of an intermediate compound can only be regarded, as Ostwald has pointed out, as a sufficient explanation of a catalytic process, when it can be demonstrated by actual experiment that the rapidity of formation of the intermediate compound and the rapidity of its decomposition into the end-products of the reaction are in sum greater than the velocity of the reaction without the formation of the intermediate body. In the case of one reaction this requirement has been fulfilled. The catalytic action of molybdic acid on the interaction of hydriodic acid and hydrogen peroxide has been explained by assuming that the first action which takes place is the formation of permolybdic acid, which then interacts with the hydrogen iodide to form water and iodine. Now it has been actually shown—(1) that permolybdic acid is formed by the action of hydrogen peroxide on molybdic acid; (2) that permolybdic acid with hydriodic acid produces water and iodine; (3) that the velocity with which these two reactions occur is much greater than the velocity of the interaction of hydrogen peroxide and hydriodic acid by themselves.

Although we may find it difficult to explain why a reaction should occur more quickly in the presence of a catalyser by the formation of these intermediate bodies, certain simple analogies may help us to comprehend how a factor which introduces no energy can yet assist the process. Thus a man might stand to all eternity before a perpendicular wall twenty feet high. Since he cannot reach its top at one jump, he is unable to get there at all. The introduction of a ladder will not in any way alter the total energy he must expend on raising his body

for twenty feet, but will enable him to attain the top. Or we might imagine a stone perched at the top of a high hill. The passive resistance of the system, the friction of the stone and its inertia, will tend to keep it at rest, even though it be on a sloping surface and, therefore, tending to slide or roll to the bottom. If, however, it be rolled to the edge, to a point where there is a sudden increase in the rapidity of slope, it may roll over, and, having once started its downward course, its momentum will carry it to the bottom. The amount of energy set free by the stone in its fall will not vary whether the course be a uniform one, or whether it falls over a precipice at one time and rolls down a gentle slope at another. It is evident that, by a mere alteration of the slope or, in the case of a chemical reaction, of the velocity of part of its course, a change in the system may be initiated and brought to a conclusion which, without this alteration, would never take place. We have, therefore, to inquire in the case of enzymes or ferments how far their action is to be explained by surface phenomena, or by the formation of intermediate compounds between the ferment and the substance it acts upon (which is generally known as the *substrate*). This discussion we may defer until the next lecture.

LECTURE II.

THE MODE OF ACTION OF FERMENTS (*continued*).

We have seen that catalytic phenomena may be explained, in part at any rate, by the formation of an intermediate compound between the catalyst and the substance or substances which are undergoing change (the substrate); and the question arises whether the action of ferments may not be accompanied by the formation of some such intermediate compound. Since the action of ferments, like that of catalysts, consists essentially in the quickening up of processes which would otherwise occur at an infinitely slow velocity, we must first inquire whether the study of the velocity of the reaction will throw any light upon the number of substances taking part in the reaction, and, therefore, upon the question whether the ferment is itself involved at some stage of the reaction. It is well known that the velocity of a reaction does depend on the number of substances involved. As an illustration, we may take first the case of a reaction involving a change in one substance. If arseniuretted hydrogen be heated, it undergoes decomposition into hydrogen and arsenic. This decomposition is not immediate, but takes a certain time, and the velocity with which the change occurs depends on the temperature. At any given temperature the amount of substance changed in the unit of time varies with the concentration of the substance. If, for instance, one-tenth of the gas be dissociated in the first minute, in the second minute a further tenth of the gas will also be dissociated. Thus, if we start

with 1,000 grammes of substance, at the end of the first minute 100 grammes will have been dissociated, and 900 of the original substance will be left. In the second minute one-tenth again of the remaining substance will be dissociated, *i.e.*, 90 grammes, leaving 810 grammes. In the third minute 81 grammes will be dissociated, leaving 729 grammes. We see, therefore, that the amount changed in the unit of time will always bear the same ratio to the whole substance which is to be changed, and will, therefore, be a *function* of the concentration of this substance. Put in the form of an equation, we may say that ϕ, the amount changed in the unit of time, will be equal to KC, where K is a constant, varying with the substance in question and with the temperature, and C represents the concentration of the substance. The equation $\phi = KC$ applies to a unimolecular reaction.

If, however, two substances are involved, the equation will be rather different. In this case the amount of change in a unit of time will be a function of the concentration of each of the substances, and the form of the equation will be

$$\phi = K\ (C_x \times C_y).$$

In the case of the unimolecular reaction, halving the concentration of the substance will halve the amount of substance changed in the unit of time. In the case of a bimolecular reaction, halving each of the substances will cause the amount of change in the unit of time to be reduced to one-quarter of its previous amount. If now either a unimolecular or a bimolecular reaction be quickened by the addition of a catalyser or ferment, and the ferment enter into combination with one of the substances at some stage of the reaction, it is evident that our equation must take account also of the concentration of the ferment or catalyser. In the case of the catalytic effect of molybdic acid on the interaction between hydrogen peroxide and HI, which we studied in the

last lecture, we saw that there was definite evidence of a reaction taking place between the molybdic acid and the peroxide, resulting in the formation of an intermediate compound, namely, permolybdic acid. Brode has shown that the interaction of the molybdic acid is revealed in the equation representing the velocity of the reaction. Without the addition of molybdic acid, the equation would be

$$\phi = K\ (C_{H_2O_2} \times C_{III}).$$

After the addition of the molybdic acid, the equation becomes

$$\phi = K\ (C_{H_2O_2} + \gamma \cdot C_{\text{molybdic acid}})\ C_{III},$$

where γ is another constant depending on the molybdic acid. If the ferments, which are engaged in the solution of the foodstuffs, act in a similar way by the formation of intermediate compounds, this fact should be revealed by a study of the velocity at which the ferment action takes place.

Various methods may be adopted for the study of the velocity of ferment in action. If, for instance, we were investigating the action of diastase upon starch, we should take solutions of starch and of diastase of known concentrations, keep them in a water bath at 38° C., or whatever temperature it is desired to study, and at a given moment add, say, 20 cc. of ferment solution to every 100 cc. of the starch solution. At periods of five or ten minutes after the addition had been made, 5 cc. of the mixture might be withdrawn by a pipette and at once run into boiling Fehling's solution. The precipitated cuprous oxide would be dried and weighed, and would give directly the amount of sugar formed in the action of the ferment. After obtaining a series of data in this way, a curve could be drawn, showing the amount of change of starch which had occurred in each unit of time. In the case of the action of invertase on cane sugar the investigation is still easier. Since the change from cane sugar to invert sugar is accompanied by a change in the rotatory power of

the solution on polarised light, it is only necessary to put the mixture of ferment and cane sugar into a polarimeter tube, which is kept at a constant temperature by means of a water jacket, and read off at intervals of a few minutes the change in the rotatory power of the solution. From this change can be easily calculated the percentage of cane sugar still present, and therefore the total amount which has been converted into fructose and glucose.

The question of the velocity of reaction becomes more complex when we deal with the proteolytic ferments, owing to the immense variety of products which result from the breaking down of a proteid and its disintegration in successive stages, albumoses being first formed, then peptones, and finally amino-acids. The matter is still further complicated by the fact that these stages are not adhered to rigidly, a certain amount of amino-acids being formed at the very beginning of the reaction. In any investigation, however, of the action of proteolytic ferments such as pepsin or trypsin, we may take any given alteration of proteid and observe the velocity with which it occurs. Thus, if we are studying the action of trypsin on caseinogen, we can take samples at five-minute intervals and run them into some substance such as trichlor-acetic acid, which will precipitate all the unchanged proteid, *i.e.*, caseinogen, but will leave in solution the products of hydration of the proteid. From the amount of nitrogen in the filtrate from the precipitate can be determined the total amount of proteid which has undergone hydration in the sample under observation. Or we may take measured portions at intervals, and judge of the amount of albumoses and peptones present by the intensity of the biuret reaction which can be obtained in each sample. This method, however, suffers from the drawback that the albumoses and peptones, at any rate in the action of trypsin, are formed merely as a

stage in the process, and the intensity of the reaction will first rise to a maximum and then gradually disappear.

In the process of proteolysis there is a breaking down of the complex colloid molecules into a large number of simpler molecules. The colloidal proteid molecule has very small conducting power for electricity. The products of its disintegration, namely, albumoses and amino-acids, belong to a class of bodies known as the amphoteric electrolytes, which have a conducting power, small in itself, but large compared with that of the original proteid molecule. Moreover, in the process of disintegration, the salts which are absorbed by the colloidal molecule, and therefore not free to exercise their conducting power, are set free. These two factors together, the production of smaller molecules and the setting free of saline electrolytes, account for the rapid rise in the conductivity of a proteid solution when it is subjected to hydrolysis. The change in conductivity can be used as a means of judging the rate of proteolysis. This method presents the great advantage that a continuous series of readings can be taken without removing the solution from the bath, and without altering in any way the chemical conditions of the solution. These observations may, moreover, be quickly carried out, so allowing a large number of comparative experiments under different conditions to be made. This method has therefore been employed by Bayliss in an investigation of the conditions which determine the velocity of action of trypsin on solutions of caseinogen.

We may consider first those experiments in which the amount of trypsin was small compared to the amount of substrate (caseinogen). In this case it was found that the velocity of reaction was independent of the concentration of the caseinogen solution, and was a direct linear function of the amount of ferment present. This is shown by the

experimental results in the following table, where is given the effect of altering the concentration of the ferment on the time taken for the hydrolysis to proceed to a certain point. The point chosen was the time taken for the conductivity to increase to 350 gemmhos (the reciprocal of the unit of resistance, megohm).

Relation to Concentration of Trypsin.

Trypsin.	Time of equal change.
40	3
20	6·5
10	10
4	40
2	75
1	150

It will be seen that the time taken for this change is inversely proportional to the concentration of the ferment.

The same result has been observed in the case of other ferments. Thus the table below shows the results obtained by E. F. Armstrong* on the hydrolysis of lactose by small quantities of lactase.

Proportions Hydrolysed in 100 cc. of a 5 per cent. Solution of Lactose.

Solutions containing—	1·5 hours.	20 hours.	45 hours.
1 cc. lactase	0·15	2·2	3·9
10 cc. ,, ...	1·6	23·3	38·6
20 cc. ,, ...	3·2	45·8	—

Here again the amount of change is proportional to the amount of ferment present. The same observer has found that, if the amount of substrate is very large compared to the ferment, increasing the concentration of the substrate does

* "Studies on Enzyme Action." Proc. Roy. Soc. Vol. LXXIII. pp. 500 *et seq.*

not increase the amount hydrolysed, *i.e.*, a given quantity of ferment is able to change only a certain amount of sugar in a given time, whatever may be the concentration of the latter. This is shown in the following table (Armstrong) :—

AMOUNT OF SUGAR (LACTOSE) HYDROLYSED.

Solutions containing—	24 hours.		46 hours.	
	Proportion.	Weight.	Proportion.	Weight.
10 per cent. lactose ..	14·2	1·42	22·2	2·22
20 ,, ,, ...	7·0	1·40	10·9	2·18
30 ,, ,, ..	4·8	1·44	7·7	2·21

Moreover, if we take only the earlier stages of the ferment action, it is found that, with small proportions of ferment, equal amounts of substrate are changed in successive intervals of time until about 10 per cent. has been hydrolysed. This is shown in the following table :—

2 PER CENT. LACTOSE WITH LACTASE.

Time.	Amount hydrolysed.
½ hour	.. 3·2
⅔ ,, ...	.. 6·4
1 ,, ...	.. 9·6
2 hours	.. 16·4
3 ,, ...	.. 20·8

Quite a different result is observed when the amount of ferment is large relatively to the amount of substrate.

EFFECT OF CONCENTRATION OF SUBSTRATE (BAYLISS).

Caseinogen, per cent.	Change in 20 minutes.
4	.. 385 gemmhos.
3·2	395
2	200
·8	110
·4	10

Thus, in the experiment of Bayliss represented here, it will be noticed that, with 2 cc. of the 2 per cent. solution of trypsin, the amount of change in twenty minutes was approximately equal in a 3 per cent. solution and in a 4 per cent. solution of caseinogen. On diminishing the amount of caseinogen so that it was 2, ·8, and ·4, he found, however, a rapidly lessening amount of change with the diminishing concentration of the caseinogen. This, of course, is what one would expect either in a unimolecular or bimolecular reaction; but if a series of observations are made at intervals of ten minutes on a mixture containing caseinogen and a proportionately large amount of ferment, it will be seen that there is a rapid diminution of the rate of change from the very beginning. This is shown in the table below, in which the velocity constant K has been calculated from a series of observations.

VELOCITY OF TRYPSIN REACTION.

6 cc. 8 per cent. caseinogen + 2 cc. $\frac{N}{10}$ AmHO + 2 cc. 2 per cent. trypsin at 39° C.

1st 10 minutes	.. ..	K = 0·0079
2nd ,,	.. ..	0·0046
3rd ,,	.. ..	·0032
4th ,,	.. ..	·0022
5th ,,	.. ..	·0016
7th ,,	.. ..	·0009
Etc.		Etc.

Whereas in an ordinary chemical reaction, such as those mentioned at the beginning of this chapter, K remains constant throughout the reaction, here we see a rapid diminution in this factor.

How are we to account for the results obtained with small and large quantities of ferment respectively? The experiments made on small quantities of ferment can only be interpreted by assuming that the first stage in the reaction

is a combination of ferment with substrate. It is only this compound which represents the *active mass* of the molecules, *i.e.*, the molecules of substrate which are undergoing change. This compound, as soon as it is formed, takes up water and breaks down, setting free the hydrolysed substrate and the ferment, which is at once ready to combine with a further portion of the substrate. In such a case the velocity of reaction must be directly proportional to the amount of ferment, and the same absolute quantity of substance will continue to be changed in succeeding units of time. Supposing, for instance, we had at the bottom of a hill a load of bricks which had to be transferred to the top, and five men to effect the transference. The rate of transference would be directly proportional to the number of men employed; we could double the rate by doubling the men. Moreover, the number of bricks carried in each unit of time would be the same. Five men would carry as many bricks in the second ten minutes as they would in the first, and so on. On the other hand, the velocity with which the transference was effected would be independent of the number, that is, the *concentration* of the bricks at the bottom of the hill. The *active mass* of bricks could be regarded as that number carried at any moment by the transferring factor, namely, the men. The equation of change would be $\phi = K C$, where C is the concentration of the ferment. This concentration is always being renewed, and kept constant by the breaking down of the intermediate product, so that the rate of change would be continuous throughout the experiment.

The condition of things which obtains when the amount of ferment is largely increased is more difficult to interpret. The rapid diminution in the velocity of change may be caused, in part at least, by the autodestruction of the ferment. All these ferments are unstable bodies, and tend to undergo

disintegration in watery solutions. That this is not the most important factor, however, is shown by the fact that, when the action of trypsin on caseinogen has apparently come to an end, it may be renewed by further dilution of the mixture or by removal of the end products of the action by dialysis. It is evident that, in this retardation of the later stages of ferment action, the end products are concerned in some way or other, and the retardation can be augmented by adding to the digesting mixture the boiled end products of a previous digestion. The retarding effect of the end products resembles in many ways that observed in a whole series of reactions which are known as reversible. As an example of such a reaction we may take the case of methyl acetate and water. When methyl acetate is mixed with water it undergoes decomposition with the formation of methyl alcohol and acetic acid. On the other hand, if acetic acid be mixed with alcohol, an interaction takes place with the formation of methyl acetate and water. These changes are represented by the equation $Me\,C_2H_3O_2 + HOH \rightleftarrows Me\,OH + HC_2H_3O_2$. Each of these changes has a certain velocity constant, and, since they are in opposite directions, there must be some equilibrium point where no change will occur, and where there will be a certain definite amount of all four substances present in the mixture, namely, water, alcohol, ester, and acid. This equilibrium point can be altered by altering the amount of any of the four substances. Thus the interaction of methyl acetate and water can be diminished to any desired extent by adding to the mixture the products of the interaction, namely, methyl alcohol and acetic acid.

The question at once arises whether we have in the action of ferments a similar reversible phenomenon. There is evidence that some of the ferment actions are reversible. Thus maltase acts on maltose with the formation of two

molecules of dextrose. If, however, the maltase be added to a concentrated solution of dextrose, we get a reverse effect, with the production of a disaccharide which has been designated as isomaltose or revertose. The addition of the proteolytic ferment, pepsin, to a strong solution of albumose and peptone causes the appearance of a precipitate, which has been called plastein, and is probably due to a reaggregation of the albumose and peptone molecules which had been separated by the process of hydrolysis. It is possible that to this reverse action is due a certain amount of the retardation observed in the action of trypsin on coagulable proteid. It is probable, however, that another factor is involved and is the more important of the two, namely, the combination of the ferment itself with the end products, and the consequent removal of the ferment from the sphere of action. Several facts speak for such a mode of explanation. Thus the action of lactase on milk sugar is not retarded by both its end products, namely, glucose and galactose, but only by galactose. In the same way the action of invertase on cane sugar is retarded by the end product fructose, but not at all by the other end product, glucose. The effect of trypsin on proteids is retarded not only by the end products of its own reaction, but also by the addition of various end products derived from the action of proteolytic ferments on other proteids.

So far, therefore, a study of the velocity of ferment actions would lead us to suspect that the ferment combines in the first place with the substrate, and that this combination is a necessary step in the alteration of the substrate. In the second place, the ferment is taken up to a certain extent by some or all of the end products, and this combination acts in opposition to the first combination, tending to remove the ferment from the sphere of action, and therefore to retard the whole reaction. Other facts can be adduced in favour of these

conclusions. Thus it has been shown that invertase ferment, which is destroyed when heated in watery solution at a temperature of 60° C., can, if a large excess of its substrate, cane sugar, be present, be heated 25° higher without undergoing destruction. The same protective effect is observed in the case of trypsin. Trypsin in watery or weakly alkaline solutions undergoes rapid decomposition. At 37° C. it may lose 50 per cent. of its proteolytic power within half an hour.* If, on the other hand, trypsin be mixed with a proteid such as egg-albumin or caseinogen, or with the products of its own action, namely albumoses and peptones, it can be kept many hours without undergoing any considerable loss of power.

Another fact, which tells in favour of some form of combination between ferment and substrate, is the specificity of the ferment; *i.e.*, each ferment will act only on a class of bodies grouped together by their chemical composition, and especially by the stereochemical configuration of their molecules. In the table on next page is drawn up a list of four ferments, with the substances with which they can combine.†

In this list it will be seen that, whereas maltase splits up all the α-glucosides, it has no power on the β-glucosides; that is to say, maltase will fit into a molecule of a certain configuration, but is powerless to affect a molecule which differs only from the first in its stereochemical structure. On the other hand, emulsin, which breaks up β-glucosides, has no influence on α-glucosides.

This specific affinity of the ferments for optically active groups of bodies suggests that the ferment itself may be optically active. We cannot of course isolate the ferment and

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* Cp. Vernon, *Journ. of Physiol.* Vol. XXVIII. p. 448, 1902.

† E. F. Armstrong, *loc. cit.* p. 520.

determine its optical behaviour, but that it is optically active is rendered probable both by these results and by certain results obtained by Dakin * on lipase, the fat-splitting ferment. Dakin carried out his experiments on the esters of mandelic acid. Mandelic acid is optically inactive, but this optically inactive modification consists of a mixture of equal parts of dextro-rotatory and lævo-rotatory mandelic acid. The esters

Enzyme.	Corresponding hydrolyte.	Effect of hexose on rate of change.		
		Glucose.	Galactose.	Fructose.
Lactase.	β - galactosides, milk sugar; β-alkylgalactosides.	No influence.	Retards.	No influence.
Emulsin.	β-glucosides (most natural glucosides); β-galactosides.	Retards considerably.	Retards slightly.	No influence.
Maltase.	α-glucosides, maltose, and α-alkylglucosides; α-galactosides (*i.e.*, α-alkylgalactosides).	Retards considerably.	Retards slightly.	No influence.
Invertase.	Fructosides; cane sugar; raffinose; gentianose.	No influence.	—	Retards.

prepared from the optically inactive acids are themselves optically inactive. Dakin found that, when an optically inactive mandelic ester was acted upon by a lipase prepared from the liver, the final results of the action were also inactive; but if the reaction were interrupted at the half-way point, the mandelic acid which had been liberated was dextro-rotatory, while the remainder of the ester was lævo-rotatory. Thus the rate of hydrolysis of the dextro-component of the ester is greater than that of the lævo-component, a result which

* Dakin, *Journ. of Physiol.* Vol. XXXII. p. 199, 1905.

can be best explained by the assumptions (*a*) that the enzyme or a substance closely associated with it is a powerfully optically active substance; (*b*) that actual combination takes place between the enzyme and the ester undergoing hydrolysis. Since the additive compounds thus formed in the case of the dextro- and lævo-components of the ester would not be optical opposites, they would be decomposed with unequal velocity, and thus account for the liberation of the optically active mandelic acid.

The scanty evidence, which we have as to the composition of ferments, would seem to point to a chemical similarity between ferment and substrate. Thus, in the case of invertase, Osborne * found that it had the composition of a carbohydrate with a nitrogenous group introduced. This similarity of structure between ferment and substrate is further supported by the results just mentioned as to the specific effect of closely related substances in inhibiting or retarding the action of the ferment (see table p. 32), *e.g.*, the fact that the action of lactase is retarded by galactose, but is uninfluenced by glucose or fructose. We may conclude that, in the action of ferments on the food substances, whether carbohydrate or proteid, an essential factor is the combination of the ferment with the substrate, and it is only the part of the substrate, which is thus in combination or in relation with the ferment, which can be regarded as the active mass and as undergoing the hydrolytic change.

These ferments however cannot be dealt with in the same way as the definite chemical substances such as molybdic acid. All of them are of a colloid or semi-colloid nature, and it is impossible to assign to them a chemical formula, or to form any idea of the actual number or condition of the molecules

* Osborne, "Zeitsch. f. Physiol. Chem.," XXVIII., p. 399, 1899.

involved in the reaction. In many cases too the substrate, *e.g.*, starch and proteid, is also of a colloidal character, and we have therefore to consider the form of interaction which can occur between such colloidal substances, and will nevertheless be specific and display the limited affinities of each body concerned.

To the relationship between ferment and substrate we have a close analogy in that between toxin and antitoxin, or between lysin and antilysin, etc. As examples of toxins we may take diphtheria and tetanus toxin. These are substances produced in the living bacilli and excreted by them into the surrounding medium. When introduced into the body, they cause injury in various ways, generally by affecting the vital activity of some special tissue or class of tissues. If small doses be injected into the body, they give rise to the production in the blood serum of an antitoxin, *i.e.*, of a substance which not only has the power of inhibiting the poisonous effect of fresh doses of toxin, but can be added to the toxin *in vitro* and neutralise its effect when injected into other animals. A close similarity exists between toxins and various other substances which are produced by bacteria and other living organisms. Thus the filtered extracts of tetanus or diphtheria bacilli, besides the specific toxins, contain bodies which have a hæmolytic action and are spoken of as hæmolysins. Similar hæmolytic substances are contained in the venom of snakes, in abrin (the poisonous proteid obtained from the plant jequirity), and in the filtered culture fluid from a species of bacillus, namely, *Bacillus megatherium*. The injection of hæmolysins into the circulation of an animal, in gradually increasing doses, gives rise to the appearance in the blood serum of an antilysin.

The most usual conception of the action of these bodies, a conception which we owe to Ehrlich, is that they consist of a

centrally placed proteid group with two side chains, one of which by its stereomeric configuration is peculiarly adapted to fit on to the organ or cell of the body which the toxin or active body attacks, and is known as the *haptophore* group, and another side chain, the *toxophore* group, which is responsible, when the toxin is once anchored, for the destructive changes wrought by the toxin on the cell of the body. The antitoxins or antilysins are thus supposed to act in virtue of their adaptation to the haptophore group, so as to combine with the toxin or lysin and prevent these exercising their injurious effects on the body. Ehrlich has shown that in many toxins the toxophore group can undergo weakening or destruction without any alteration of the haptophore group; such modifications he designates as *toxoids*. They have the same combining power for antitoxins as is possessed by the ordinary toxin, but are either without physiological effect, or their poisonous characters are only a fraction of that possessed by ordinary toxin. It seems probable that in the case of enzymes we have also to deal with similar relationships. We may conceive that the ferment fits on, as we have seen really happens, by means of its haptophore group. The specificity of the enzyme is therefore a function of its haptophore group. The changes it effects in the substrate would be due to a zymophore group. As in the case of toxins, this zymophore group may undergo alteration or destruction without the haptophore group, and modifications of enzymes may be produced by heating or other means, resulting in the production of a substance which may be termed *zymoid*. Thus Bayliss has shown that trypsin on warming, or under the action of strong acid, is converted into a modification which has much less proteolytic power than ordinary trypsin, but still possesses the power of binding certain molecules of the substrate. This combining effect is shown by the fact that the addition of the zymoid to a

proteid solution causes a preliminary fall in the conductivity of the whole solution. It has been shown moreover by Korschun, that from rennin ferment it is possible, by filtration through a clay filter, to separate a part which has less coagulating power on milk than ordinary rennin, but has the same power of neutralising an anti-rennin serum produced by the injection of rennin into the veins of an animal.

The question of the manner in which the antitoxin is able to combine with and neutralise the toxin is one of considerable practical importance. In this process we have relations presenting marked analogies with the neutralisation of acids by bases. If we define a unit of toxin as that amount which possesses a certain power, *i.e.*, which will kill a guinea-pig in so many days, or will cause the complete hæmolysis of 1 cc. of blood in two and a half hours, we can find the amount of anti-body which is just sufficient to neutralise this effect, and this amount of anti-body can be regarded also as one unit. If instead of one unit of each we take 100 units, the neutralisation is effected in the same way. The process is found, however, to be more complex when we take 100 units of toxin or lysin, and attempt to neutralise them by the fractional addition of antitoxin. In the case of a strong acid and strong alkali we know that, if 100 cc. of alkali are just sufficient to neutralise 100 cc. of acid, the addition of 50 cc. of alkali will leave half the acid unneutralised. If, however, we try the same experiment in the case of mixtures of toxin and antitoxin, it will be found that the addition of 50 cc. of antitoxin will neutralise much more than half of the toxin, and the same applies with other bodies of this class. As an example, we may take the relation between a standard suspension of typhoid bacilli and a serum which has the power of agglutinating typhoid bacilli. In the table given below are represented the results of the addition of varying

units of agglutinating serum to a suspension of bacilli. It will be seen that the amount taken up by the bacilli is not a definite quantity, but is determined by the concentration of the agglutinating solution.

Effects of Adding Various Dilutions of Agglutinating Serum to Equal Volumes of a Suspension of Typhoid Bacilli. (Craw.)

Concentration of Serum.	Units of agglutinin added.	Units of agglutinin absorbed.	Units of agglutinin free.
1/20	2000	1300	730
1/30	1333	1133	200
1/40	1000	840	160
1/60	666	646	20
1/200	200	200	0

Ehrlich has attempted to explain this result by assuming that in any toxin there is a mixture of substances, some having a strong affinity for the antitoxin, and others, which he calls toxones, possessing only a slight affinity. In the 50 cc. of toxin first added, the toxins would satisfy all their combining powers, whereas the toxones would not begin to combine until they were present in large excess. Arrhenius and Madsen have drawn an analogy between the neutralisation of toxin by antitoxin and the neutralisation of a weak acid, such as boracic acid, by a weak base, such as ammonia. They show that in this case the general course of events would be similar to that observed by Ehrlich. At no time would there be complete neutralisation, owing to the fact that hydrolysis constantly occurs, so that, when equivalent quantities of each substance had been added, the fluid would still contain a certain amount of free base alongside of free

acid, in addition to the salt produced by the combination of the two. It is impossible, however, to account for all the phenomena presented in the neutralisation of toxin by antitoxin in this simple manner. Thus the results given in the above table could not be explained on any hypothesis of chemical combination. Seventeen parts of ammonia would neutralise exactly an equivalent quantity of boracic acid, whether these substances were dissolved in 10 cc. or in 100 cc. of water. If, however, it be found that 1 cc. of antilysin exactly neutralises 1 cc. of lysin, these two substances will no longer be in equilibrium when the whole is diluted up to 10 cc. with water. If a neutral mixture of lysin and antilysin be taken and filtered under pressure through a gelatin filter, no lysin or antilysin passes through the filter, so that the residue on the filter becomes concentrated. On examining this residue it is found that it has a strong hæmolytic action, and the same is true of the substance which may be obtained by melting the gelatin out of the pores of the filter. It is evident that, even in a neutralised mixture, both free lysin and free antilysin, or free toxin and free antitoxin are present, and it needs only the alteration of the physical conditions of the mixture in order to display the action of one or other of these bodies. How then are we to regard this combination of toxin with antitoxin? Craw points out that the combination is in all respects comparable to that which occurs between adsorbing surfaces and many dye-stuffs. If we place some filter paper in a solution of fuchsin or Congo red, the filter paper will take up a large amount of the dye substance. The amount taken up by the paper will increase with increase in concentration of the solution. There will, however, be a tendency to the formation of false equilibrium points, as in the case of the reaction of toxin and antitoxin. Thus if two solutions of fuchsin be made,

and to each a sheet of filter paper be added, but in one case the paper be added at once, in the other case in three parts at intervals of twelve hours, at the end of thirty-six hours the paper which has been added in parts will have removed more dye-stuff from the solution than is the case where the whole amount of paper was added at once. In the same way, when treating a suspension of bacilli with an agglutinating serum, it is found that the successive addition of the bacillary suspension to the serum removes more agglutinin from the solution than when the addition is made at one time.

The interactions, therefore, between these bodies must be looked upon as special examples of the group of phenomena known as adsorption, such as the adsorption of iodine from solutions by charcoal, of iodine from water by starch, or of ammonia by charcoal.

Is the combination between ferment and substrate of the same nature? Though it is impossible to give a decisive answer to this question at the present time, it seems probable that the specific combination of ferments with certain definite substrates is in all respects analogous to the combination of toxin or lysin with their corresponding anti-body, and it is noteworthy that the assumption of the colloidal condition—a condition in which there is an enormous exaggeration of surface—seems to be an important condition in deciding the catalytic effect of any given substance. Thus platinum, which, in the metallic state, has a marked power of condensing oxygen and hydrogen on its surface, has also a strong catalytic action. The same catalytic power can be imparted to other metals such as gold, silver, lead, cadmium, or silver, by bringing them into colloidal solution. As Bredig has shown, the passage of a small arc between metallic wires under distilled water leads to the metal being thrown off in clouds of fine ultra-microscopic particles, which remain in perpetual

suspension in the fluid. The 'sol' thus obtained has all the properties of a colloidal solution, and it shares with platinum 'sol' the power of quickening various chemical processes, especially the decomposition of hydrogen peroxide. We know that the molecules which are in immediate contact with a surface are in a different condition of aggregation, and the mere exaggeration of surface, which occurs in these colloidal solutions, seems to be sufficient to bring a large number of molecules into the condition in which they are able to interact chemically, and so hasten any chemical interaction which would otherwise go on with an extremely slow velocity. This influence of surface is not, however, absolutely general. Even platinum 'sol' is not a universal catalyser, and although in every case we must regard adsorption by a surface as the essential factor, the exact adsorption which takes place is evidently a function of the chemical configuration of the substance forming the surface. We cannot otherwise account for the specific interaction between toxins and antitoxins, or for the specific action of the different ferments on their various substrates. We have here, therefore, a special class of interactions, not entirely chemical and not entirely physical, but depending for their existence on a co-operation of both chemical and physical factors. To definitely assign ferment actions to this class would be premature. There is, indeed, evidence that ferments act on the substrate by forming intermediate combinations with it, but whether these compounds are to be regarded as chemical or as adsorptive we have not yet sufficient evidence to determine. The facts that the ferments all belong to the class of imperfect colloids, and that in many cases, *e.g.* proteolytic ferments and diastase, their action is on complete colloids, would certainly suggest that the combinations must be of the physical type.

LECTURE III.

SECRETION OF SALIVA.

The taking of food into the mouth is at once followed by the pouring out of a large quantity of saliva into this cavity. This fluid is the product of secretion, partly of a multitude of small glands scattered over the surface of the tongue and the mucous membrane forming the lining of the mouth cavity, but to a larger extent of three pairs of salivary glands which pour their fluid into the mouth by means of long tubes or ducts. These glands are the parotid, the submaxillary, and the sublingual. The fluid which moistens the food is therefore a mixture of the secretions of these various glands. Its average composition has been given by Maly as follows:—

Water	992·9
Total solids	7·1
Suspended solids (epithelium, mucus, etc.)	1·4
Soluble organic matter (chiefly proteid and mucin) ..	3·8
Inorganic salts	1·9

The composition, however, varies according to the nature of the food which has been taken in.

The use of this admixture of food with saliva is chiefly mechanical. The saliva not only moistens the food and thus aids its mastication by the teeth, but also, in virtue of the mucin that it contains, lubricates all the passages, and so facilitates the process of swallowing, and the passage of the food bolus into the stomach. In dogs the mechanical action of saliva is its only one. In herbivora and in omnivora, such

as man, the saliva has a further action, and is an important agent in the digestion of starch. The saliva secreted by the parotid gland contains an amylase known as ptyalin. Under the action of this ferment, boiled starch is transformed into dextrin and maltase. It might be thought that the stay of the food in the mouth is of too short duration to admit of any appreciable degree of starch solution taking place. The action of saliva is not, however, confined to the period that the food remains in the mouth. When a meal is taken, the food, after mastication, is swallowed in a succession of boluses, and collects in a mass, moistened throughout with saliva, in the stomach. It is true that the taking of food determines the pouring out of an acid juice in the stomach, a juice which not only prevents the digestive action of ptyalin but actually destroys this ferment. It takes, however, a considerable time for this acid gastric secretion to penetrate the mass of food lying in the stomach, and the saliva in the interior of the mass has from twenty to forty minutes at its disposal to act on the starchy constituents of the food, before the acid gastric juice can penetrate and destroy the ptyalin. The main digestive action of saliva therefore occurs in the stomach.

The mixed saliva, whose composition I have given above, is the product of secretion of the different glands, and is composed of fluids which vary in their composition according to the gland from which they are derived, and according to the conditions which have determined the activity of the gland. Thus the saliva obtained from the parotid gland contains water, salts, traces of albumin and globulin, and in many animals ptyalin. Mucin is however absent. On the other hand, the secretion of the submaxillary gland, especially in the dog, consists essentially of a solution of mucin in a weak salt solution. This secretion can vary considerably in quality according to the conditions determining the activity of the

gland. Thus by a suitable admixture of these various secretions it is possible to adapt the saliva to the nature of the food in the mouth. In order to determine the nature of the saliva which is poured into the mouth in response to the physiological stimuli of various kinds of food, the best method is to divert the ducts of the submaxillary and parotid glands and make them open on the exterior of the cheek.* By attaching receptacles to the orifices of these displaced ducts, it is possible to collect separately the saliva of each gland and to study its modifications with variations in the food. By such means it has been found by Pawlow that, on administration of meat to a dog, the saliva which is secreted is derived mainly from the submaxillary gland and is thick and viscid, containing a relatively large amount of mucin. If, on the other hand, dry powdered biscuit be introduced, the resulting secretion is thin and watery, and is obtained from both sets of glands. The introduction of stones into the animal's mouth evokes no secretion at all. The animal can get rid of the stones by movements of the tongue without any preliminary moistening. The introduction of sand into the animal's mouth is, however, followed by a copious secretion of a thin watery saliva, which serves the purpose of washing the sand from the surface of the mouth and enabling this substance to be rejected by the animal. These facts reveal a differential activity of these glands according to the needs of the animal. Such a differential secretion, adapted as it is to the nature of the substances present in the mouth, involves the intermediation of some complex reactive mechanism, and the rapidity with which the reaction takes place indicates that we must seek for the mechanism in the central nervous system—that, in fact, we

* This method, which has been much employed by Pawlow, was first used by De Graaf, as will be seen from the figure on p. 81.

have here a complex reflex arc. The nervous channels of the reflex have been determined in the case of all three pairs of salivary glands. The afferent channels are represented by the special gustatory nerves, as well as the nerves of common sensation, which run chiefly in the fifth and ninth cranial nerves to the brain. The efferent channels vary in the case of the different glands. Each gland receives a double nerve supply, viz., from the cranial nerves and from the sympathetic system. The impulses which travel along the sympathetic pass out from the spinal cord along the upper two or three dorsal nerve roots; thence they travel in the cervical sympathetic to the superior cervical ganglia. Here there is a new relay of fibres, which start from the cells of the ganglia and travel up in the walls of the branches of the external carotid artery to be distributed with the arteries to the salivary glands. The cranial supply of the parotid gland arises from the ninth nerve and passes through the tympanic plexus into branches of the fifth nerve, with which it is distributed to the gland. The fibres to the submaxillary and sublingual glands leave the brain with the intermediate nerve of Wrisburg and pass with the facial into the chorda tympani, the branches of which nerve carry the impulses to the gland. The centre must be located somewhere in the lower part of the cranial axis, in the neighbourhood of the pons and medulla.

This reflex mechanism can be set into activity, not only by stimuli applied to the surface of the mouth, but also, in default of such stimuli, by processes which must be located in the cortex cerebri. Pawlow has shown that the specific secretion is evoked, not only by the introduction of different substances such as meat, biscuit powder, or sand into the dog's mouth, but also by merely showing the dog the substances in question, so that the calling up of the psychical images of these substances has the same effect as their actual introduction into

into the mouth. As soon as the animal realises that it is being played with, and that there is no intention of really giving it these things, the psychical secretion of saliva ceases.

What is the mechanism of this secretion? What are the changes which are actually responsible in each gland for the production of a secretion? The chief experiments bearing on the mechanism of secretion have been made upon the salivary gland, since this forms a compact organ, which can be easily isolated from other tissues without injury to its blood and nerve supply. Moreover, a state of activity is readily induced in the gland, either by the injection of drugs such as pilocarpin, or by excitation of its nerves, which are easily accessible. In investigating the action of its nerves upon the gland, a small tube or cannula is placed in the duct, so that the saliva can be led off and measured and its qualities determined. At the same time the chorda tympani and the sympathetic nerves are dissected out and prepared so that they can be stimulated electrically. It is found that these two sets of fibres differ in their results on the gland. The stimulation of the peripheral end of the chorda is at once followed by a copious flow of thin watery saliva which contains only a small amount of mucin. There is also great dilatation of all the arterioles of the gland, so that the blood-flow through it is increased five- to eight-fold. Stimulation of the sympathetic evokes a scanty secretion of thick viscid saliva, generally opalescent in appearance and containing a relatively large amount of mucin. On the blood-vessels the action of the sympathetic is the reverse of that on the chorda. The sympathetic carries vaso-constrictor fibres to all parts of the head and neck. The arterioles of the gland are therefore constricted, and the flow of blood through the gland very largely reduced.

The question arises whether, in these two sets of nerves, we have two distinct varieties of secretory fibres influencing

different parts of the gland cells, or whether the differences between the two kinds of secretion may not be determined by the coincident changes in the blood supply. Heidenhain stated that the histological results of stimulating the sympathetic nerve were much more pronounced than those obtained by stimulating the chorda tympani, and suggested that the nerves to the glands ought to be divided into two classes, namely (1) trophic nerves, *e.g.*, sympathetic, which influence chiefly the metabolic changes in the cells themselves, and (2) secreto-motor fibres, which determine the secretion of water and salt by the glands. Langley however has been unable to confirm the statement of Heidenhain as to the peculiar effects of the sympathetic on the structure of the glands. According to Langley the histological results of stimulating either set of fibres are of the same order. On the other hand, the secretion obtained on stimulating the chorda can be approximated to sympathetic saliva by diminishing the blood flow to the gland, while secretion is going on, either by clamping of the arteries or by bleeding the animal. Under these conditions the saliva becomes thicker and more viscid, and its percentage of solids increases. Langley therefore is inclined to regard all the fibres going to the gland as of essentially the same character, namely secretory; and considers the differences between the two kinds of saliva as determined entirely by the concurrent vascular changes induced by stimulation of the two sets of nerves. It has been urged against this view of the identity of the chorda and sympathetic secretory fibres that, whereas the chorda fibres are paralysed by a minute dose of atropin, it is very difficult to affect the action of the sympathetic even by large doses of this drug. This difference in the susceptibility of the two sets of fibres to the action of atropin might however point to a morphological rather than to a functional distinction. For the present, therefore, we may

regard the glands as supplied by one kind of fibre, namely secretory, in addition to the fibres which exercise their main influence on the blood-vessels of the gland ; and we may treat the effects of stimulation of the chorda tympani as typical of the state of activity of the gland.

On investigating the conditions of secretion, it very soon becomes manifest that this process cannot be determined by the blood pressure within the blood capillaries of the gland, however much the changes in the blood supply may modify the character of the secretion. Saliva cannot be regarded as a simple filtrate from the blood circulating through the glands. This is shown, in the first place, by the specific composition of the saliva. Although amylase, albumin, and globulin, as well as salts, are present in the surrounding plasma, this fluid contains no trace of mucin. Moreover, though it is possible, under a pressure comparable to that in the blood capillaries, to separate by filtration from the blood plasma a fluid containing only the water and salts of the plasma, it would be impossible to separate off a salt solution of the composition of saliva without the application of a force far transcending in extent even the arterial blood pressure. Whereas blood plasma contains a mixture of salts in such proportions as to be isotonic with a ·9 per cent. solution of sodium chloride, the concentration of salts in the saliva is only equivalent to about ·45 per cent. sodium chloride, or even less, *i.e.*, the molecular concentration of the saliva is only about half that of the blood plasma. Even supposing that we could conceive of a filter capable of keeping back one-half the salts of the blood plasma, it would require a pressure of several atmospheres in order to effect the separation and to force any fluid at all through the filter. The osmotic pressure of the blood plasma is about 4,500 mm. Hg. The osmotic pressure of the saliva would be less than 3,000 mm. Hg., so that a minimum

pressure of 1,500 mm. Hg., *i.e.*, two atmospheres, would be necessary to effect the separation of a fluid from blood plasma having the molecular concentration of saliva.

The impossibility of explaining the process of secretion as in any way determined by the blood pressure was pointed out long ago by Carl Ludwig. Ludwig showed that, if a mercurial manometer be connected with the carotid artery of an animal, and another with a cannula placed in the duct of the sub-maxillary gland, the occurrence of secretion on stimulation of the chorda causes the manometer attached to the duct to rise to a height much greater than that of the manometer connected with the carotid artery. While the blood pressure in the arteries going to the gland may be 120 mm. Hg., the pressure in the salivary duct may rise to 210 mm. Hg. This experiment proves conclusively that, somewhere between blood-vessels and duct, there must be living cells which are themselves taking an active part in the process of secretion, and furnishing energy for the process—energy which can be derived only from the metabolism of the cells, and ultimately from the oxidation of their food-stuffs.

Between the blood and the duct there are two layers of cells, namely the delicate endothelial cells forming the capillary wall, and the much larger cells which form a continuous lining to the ultimate ramifications of the gland-ducts, the alveoli. It has often been suggested that, in the process of secretion, the endothelial cells and vessels must take an important part, and this view was not directly negatived by the action of atropin. Atropin, as is well known, prevents altogether the action of the chorda tympani upon secretion, *i.e.*, it paralyses the secretory fibres of the chorda tympani. It has no action, however, upon the vaso-dilator fibres of this nerve, so that stimulation of the chorda after administration of atropin evokes an increased flow of blood through the gland

without any corresponding secretion. The absence of secretion might be ascribed equally well to an action upon the endothelial cells of the vessels as to an action upon the cells of the secreting alveoli. To decide this point Gianuzzi attempted to paralyse the secretory cells by the injection of acid into the duct. On then stimulating the chorda tympani no secretion was obtained, but the gland swelled up and became œdematous. This observer concluded that the effect of the injection of the acid was to paralyse the secretory cells of the gland, without paralysing the process of secretion as effected by the endothelial cells and blood-vessels. This explanation is, however, incorrect. The injection of acid injures, not only the cells of the alveoli, but also the endothelial cells of the blood-vessels, and, as in any other injury, the production of vaso-dilatation causes a copious transudation of lymph through the injured vessel wall, and therefore the production of œdema. A consideration of the other changes occurring in the gland coincidently with secretion shows conclusively that the active cells are not the vascular endothelium, but the cells lining the alveoli themselves. In the process of secretion there is an evolution of energy. We have to determine the seat and conditions of production of this energy. In order to do this, we must examine more carefully the various changes which occur in the gland concurrently with the process of secretion.

1. *Blood-flow through the Gland.*—We have already seen that stimulation of the chorda tympani nerve causes active vaso-dilatation in the vessels of the gland, and a largely increased flow of blood through this organ. The same quickening of the blood-flow is observed when the gland is excited to secrete reflexly, by the application of stimuli to the mucous membrane of the mouth, or by the injection of drugs such as pilocarpin. During active secretion the blood-flow

through the vessels of the gland is increased on the average to five times the amount which obtains during rest.

As a result of stimulation a very large amount of water is turned out through the gland ducts. In one experiment of Heidenhain's* 220 cc. of saliva were secreted by a gland weighing about 6 grammes. This water cannot come from the gland itself, and must therefore be furnished ultimately by the blood which circulates through the vessels of the gland. The loss of water by the blood in passing through the gland has been determined by Barcroft,† who estimated the amount of hæmoglobin in the arterial blood and in the blood which had flowed through the gland, taking into account at the same time the variations in the rate of flow through the gland. In this way it is possible to compare the quantity of fluid, which has been turned out by the gland as saliva, with that which has been taken up by the gland from the blood. The amount of water which leaves the blood may be considerable, so that the blood may be concentrated by as much as 25 per cent., and Barcroft has shown that the volume of water leaving the blood is always somewhat greater than that of the saliva secreted. Thus in one experiment the water lost by the blood during seven minutes amounted to 3·88 cc., while the saliva secreted during the same period was only 3·52 cc. In this case the ratio of water lost by the blood to the water in the saliva was as 1·12 to 1, and in all Barcroft's experiments the water lost by the blood was about 10 per cent. greater than the water leaving the gland in the saliva. The question arises as to the destination of this excess of water which leaves the blood-vessels. It does not remain in the gland. If a gland be stimulated for some time, it is always found to diminish in size and in weight. In two experiments

* *Hermann's Handbook*, Vol. V. (1), 1883.

† *Journ. of Physiol.* Vol. XXV., p. 479, 1900.

by Heidenhain, the right gland was extirpated and weighed, and then the left chorda tympani was stimulated for several hours. The saliva secreted was measured, and at the end of the experiment the left gland was cut out and weighed. The results of these two experiments were as follows:—

Saliva.	Right gland.	Left gland.
75 cc.	6·86 g.	5·42 g.
220 cc.	6·36 g.	5·91 g.

In each case there was a considerable loss of weight, and this loss of weight affected the solids of the gland even more than its fluid constituents. The resting glands contained 28·3 per cent. total solids, whereas the two active glands gave only 21·3 per cent. It is evident that all the water which leaves the blood must leave the gland, and the destiny of this water is at once revealed on examination of the lymph flowing from the gland. The lymph passes out by the lymphatic vessels in the hilus of the gland, and finally makes its way into the cervical lymphatic trunk. If the other vessels passing into this trunk be ligatured, a cannula can be placed in the trunk towards the head, and the lymph-flow obtained will represent the lymph from the submaxillary gland. This experiment has been performed by Bainbridge, who finds that the amount of lymph, which is practically negligible in the resting gland, is markedly increased when secretion takes place. The total quantity of lymph is about one-tenth of the volume of saliva secreted at the same time, so that, together with the saliva, it exactly corresponds to the volume of water lost by the blood in passing through the gland (Figs. 1 and 2).

It might be imagined that this increased flow of lymph during secretion was in favour of the view put forward by Gianuzzi, *i.e.*, that the first factor in secretion was an alteration of the endothelial cells of the blood-vessels and

an increased transudation. That this explanation, however, is not correct is shown by some experiments of Bunch, carried out in this laboratory, on the changes in volume of

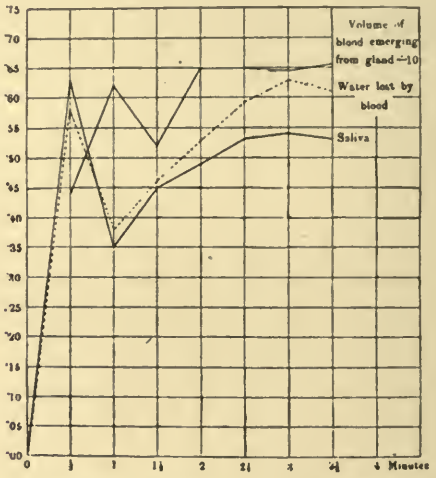

FIG. 1. — Diagram showing: (*a*) Total blood flow through submaxillary gland. (*b*) Total amount of water transferred from blood to gland. (*c*) Total secretion of saliva (Barcroft).

the gland during secretion. In these experiments the whole submaxillary gland was placed in a plethysmograph, and

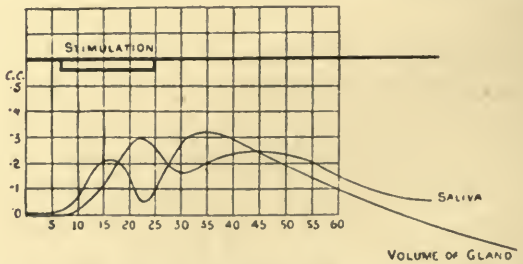

FIG. 2.—Comparison of changes in volume of submaxillary gland with the outflow of saliva produced by stimulation of the chorda tympani nerve (Bunch).

its volume recorded by connecting the plethysmograph with a piston recorder writing on a blackened surface. When vasodilatation occurs in any organ, the volume of the blood-vessels is increased, and therefore one would expect that the vasodilatation, which accompanies activity of the salivary gland, would occasion an increase in the volume of the gland. This is the case in a gland in which the chorda tympani nerve

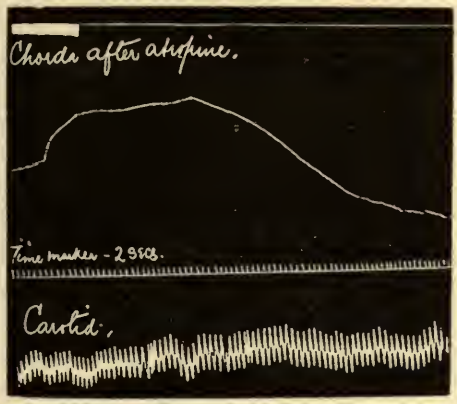

FIG. 3.—Tracing of volume of submaxillary gland, showing effect of stimulation of the chorda after administration of 10 mg. atropine. The blood pressure (lowest line) was unaltered by the stimulation (Bunch).

is stimulated, after paralysis of its secretory fibres by the administration of a small dose of atropine. The vasodilatation which results gives an increase in the volume of the gland and a rise in the recording lever (Fig. 3.) The same increase in the volume of vessels must be present when secretion is allowed to take place; but a record of the volume of the gland during normal secretion shows that the first effect is a *diminution* and not an increase, as is shown in Fig. 4. If the duct be clamped so as to prevent the escape of saliva, stimulation of the chorda gives merely an increase

in volume (Fig. 5). The diminution in volume observed when the duct is free shows—

(1) That the first result of exciting the secretory nerves is an emptying out of the contents of the gland;

(2) That this discharge of the contents of the gland, as saliva, is more than sufficient to counterbalance the swelling of the gland, produced by the dilatation of its blood-vessels.

FIG. 4.—Tracing of volume of submaxillary gland showing *decrease* on excitation of chorda. The duct was free (Bunch).

A primary increased transudation of lymph would cause an initial *expansion* in the volume of the gland, and we must conclude, therefore, that the first effect of stimulation is not on the blood-vessels, but on the secreting cells of the alveoli, causing them to empty out their contents, including solids and water. Only later can the cells recoup themselves at the expense of an increased transudation from the blood-vessels.

This loss of gland substance is indicated by the figures I

have quoted above on the changes in the weight and in the percentage of solids of the gland during secretion. The same conclusion is borne out by Pawlow's estimations of the amount of nitrogen in secreting and resting glands respectively. This observer found that, whereas ten resting glands contained 2·18 gr. of nitrogen, ten glands from the same animals, which had been stimulated for some hours, contained only 1·872 gr. of nitrogen, representing a loss by these glands during

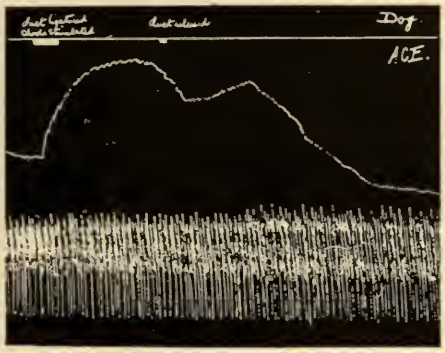

Fig. 5.—Tracing of volume of submaxillary gland, showing effect of chorda stimulation after obstruction of the duct. It will be noticed the volume diminished as soon as the duct was released, so as to allow the saliva to flow away.

secretion of ·308 gr. of nitrogen. The saliva obtained during these experiments yielded ·416 gr. of nitrogen, so that the glands had taken up only ·19 gr. of nitrogen (*i.e.*, $\frac{1}{21}$ of the total amount) from the blood passing through them. Thus the primary result of stimulating the secretory nerves is to cause the gland cells to discharge their organic matter together with water and salts. The cells then recoup themselves at the expense of the blood circulating through the blood-vessels; but this process, although practically complete in the case of

the water and salts, is very inadequate in the case of the nitrogenous constituents of the cells, which have been lost in the saliva. It is on this account that the phenomena of exhaustion occur on prolonged secretion.

A study of the histological changes occurring in the cells of the alveoli during secretion points to the same conclusions. If the salivary glands, whether parotid or submaxillary, serous or mucous, be teazed with salt solution or serum and examined under the microscope, the appearances observed will differ according to the state of activity of the gland from which the specimens have been made. If obtained from a resting gland, the cells are swollen and packed full of granules, coarse in the case of the mucous glands, fine in the case of the serous glands. The unaltered protoplasm of the cell is small in amount and situated chiefly at the periphery, away from the lumen of the alveolus. The nucleus, if brought into view by the addition of reagents, is embedded in the peripheral zone or is crushed against the basement membrane, and becomes easily shrivelled under the action of hardening reagents. If, however, the cells examined be taken from a gland which has been secreting for some hours, they present a totally different appearance. The cells are now considerably smaller in size; the granules are reduced in number, and are confined to the part of the cell immediately abutting on the lumen. The protoplasm has increased in amount both relatively and absolutely, and the nucleus is swollen and occupies a more central position in the cell. Histologically, then, secretion consists in—

(1) A discharge of the granules.

(2) A growth of protoplasm; and

(3) Changes in the appearance of the nucleus.

During rest we must assume the occurrence of reverse changes, namely, a gradual conversion of the protoplasm into granules and the accumulation of these granules in the cell,

until it is distended with them and swollen. The granules must therefore be taken as representing the precursor of the secretion. In them occur the changes which lead to the taking up of water and the discharge of the granules, dissolved and perhaps changed in character, into the lumen of the secreting alveoli.

We have already learnt that there is an expenditure of energy in the act of secretion, and it is important that we should be able to arrive at some idea of the extent of these energy changes. The energy balance of the whole body is most easily obtained by an examination either of the total potential energy presented to the body in the shape of food, or better by an analysis of the excreta consisting of carbon dioxide, water, and nitrogenous end-products such as urea. Nine-tenths of the total energy set free in the body by the combustion of the foodstuffs is represented by the carbon dioxide output of the body. We can therefore probably arrive at a fairly true idea of the energy changes in the submaxillary gland by examining its intake of oxygen and its output of carbon dioxide. In the whole body these two amounts correspond, though there is always a small loss of oxygen, about one-fifth of the whole, which is required for the oxidation of substances other than carbon in the body. When, however, we are dealing with an isolated organ, the oxygen intake is considerably more valuable than the carbon dioxide output. There is no evidence that the body in any of its tissues is able to store oxygen,* so that the intake of oxygen must be proportional at any time to the requirements of the body. On the other hand, all the alkaline juices

* Many physiologists might not agree with this statement. All would agree, however, that the power of living tissues to store oxygen is extremely limited.

of the body contain carbonates or bicarbonates. Any change in reaction of these fluids will alter their power of taking up carbon dioxide, and the mere production of acid may therefore give rise to an evolution of CO_2 which has not been immediately formed by the cells. On the other hand, increased alkalinity of the juices will enable these to take up more CO_2, and prevent therefore the output of carbon dioxide to the blood circulating through the capillary vessels.

The question of the gaseous exchanges of the submaxillary gland has been investigated by Barcroft.* The following table represents the average figures obtained from a number of observations. In these experiments the blood gases were estimated in the arterial blood and also in samples of blood obtained from the veins of the submaxillary gland. From the difference between these two figures it was possible to reckon the amount of oxygen taken up and the amount of carbon dioxide discharged.

Gaseous Exchange of Submaxillary Gland (Barcroft).

	O_2 taken up.	CO_2 output.
Resting ..	·25 cc. per minute. ..	·17 cc. per minute.
Active ..	·86 cc. ,, ..	·39 cc. ,,

It will be observed that, whereas the flow of blood through the gland may be increased five or six times during activity, the quantity of oxygen taken up by the cells is increased about three and a half times. Although the total loss of oxygen from blood to gland is increased, the relative loss is diminished, and the blood flowing from the veins of a gland during activity is more arterial in colour and contains more oxygen than the blood obtained from a resting gland. If we assume that the total oxygen taken up is employed in the oxidation of a food substance such as glucose, and that the

* *Journ. of Physiol.* Vol. XXVII., p. 31, 1901.

whole of the energy of the chemical changes is set free in the form of heat, we find that a resting gland weighing about 6 grammes produces about 1·1 calories per minute, whereas an active gland produces about 3·8 calories per minute. We know, however, that a certain amount of external work is performed in the secretion of a saliva containing less salts than the original blood, and also, when there is any resistance to the flow of saliva through the duct, in raising the hydrostatic pressure of the saliva in the duct to a height greater than that in the blood capillaries.

Can we from all these data form a conception of the total changes occurring in the gland and involved in the formation of the secretion? Even during rest, changes are going on in the gland cells, changes which involve the taking up of food material and its assimilation under the influence of the nucleus, perhaps into the nucleus itself, and certainly into the undifferentiated cytoplasm. In this cytoplasm a further change occurs, leading to its transformation into granules. When activity is excited by the stimulation of secretory nerves, the primary change appears to involve simply the granules. These structures must absorb water, apparently against osmotic pressure. Those nearest the lumen swell up, become converted into spheres containing water and salts in smaller proportion than exists in the lymph bathing the cells (and presumably in the protoplasm surrounding the granules), and in this swollen form are discharged or ruptured on the periphery of the cell into the lumen, so giving rise to secretion. This discharge of a fluid with a smaller molecular concentration than the cell or surrounding blood plasma must lead to an increased concentration in the remaining parts of the cell. The increased concentration would naturally induce a flow of water from lymph into cell, and the consequent concentration of the lymph would

in the same way cause a flow of water from blood to lymph. This pull of water by the cell from the blood is still further increased in another way. The act of secretion, involving as it does the expenditure of energy, can be carried out only at the expense of chemical changes in the cell. These chemical changes, as in all other metabolic processes of the body, will result in the formation of a number of small molecules from the great colloid molecules of the protoplasm with its side-chains. The products of metabolism, or *metabolites*, will therefore accumulate in the cell, pass into the lymph, and increase the concentration of the latter. The increased concentration will call forth an increased transudation of fluid, *e.g.*, water, from the blood vessels, and the transudation thus evoked will be greater than that necessary to provide the water of the saliva, and will therefore produce a distension of the lymphatic spaces of the gland, and an increased discharge of lymph along its efferent lymphatics. As a secondary result of the activity, perhaps in consequence of the removal of the products of the resting metabolism of the gland, there is increased growth of protoplasm, increased activity of the nucleus, and therefore a tendency to increased assimilatory changes and a preparation of the cell for further secretory changes either immediately or hereafter.

In the gland however, as in muscle, when we attempt to form a conception of the mechanism of the chemical machine in the living cell, we are brought up against insuperable difficulties. One might perhaps conceive of the secretory granules being bounded by a membrane, impermeable to intermediate metabolites and salts, but permeable to carbon dioxide. If the first effect of stimulation of the secretory nerves were to produce an explosive disintegration of the complex molecules making up the granules, we should have a sudden multiplication of molecules within the granules. This would cause a

large rise of the osmotic pressure in these granules and the consequent absorption of water from the surrounding protoplasm. This process however could only result in the production of a fluid in the granules, having the same osmotic pressure as the surrounding medium, whereas we know that saliva has a molecular concentration which is only one-half that of the blood or lymph. We should therefore have to make a second assumption; namely, that, before the extrusion of the solution from the granules, there is a further breakdown of the metabolites by a process of oxidation, with the production of carbon dioxide which diffuses into the surrounding protoplasm. We have however no evidence of either of these processes or for any of these assumptions, and I have only adduced them in order to show how far we are still from the actual comprehension of the events occurring in every living cell, and determining its conditions of rest and activity.

LECTURE IV.

DIGESTION IN THE STOMACH.

The food, which has been masticated in the mouth and thoroughly moistened with saliva, is swallowed at successive intervals, and collects to form a mass lying in the fundus of the stomach. This mass, impregnated with saliva and kept at the body temperature, is penetrated only with difficulty by any juice secreted in the stomach, so that, in those animals whose saliva contains ptyalin, the process of salivary digestion can go on unchecked, at any rate in the centre of the mass, for twenty to forty minutes.

Even before the food reaches the stomach, a special digestive fluid, the gastric juice, is poured out into the stomach. This juice is strongly acid in character. As it penetrates the mass of food, the acid first checks the action of the ptyalin and finally destroys it. The gastric juice is the product of secretion of a number of tubular glands, which are set thickly over the whole surface of the stomach, and form the greater part of the mucous membrane. On examining the internal surface of the stomach, there is seen to be a difference between the appearance of the mucous membrane over the four-fifths of the stomach nearest to the cardiac end and that covering the fifth immediately adjoining the pyloric orifice. In the latter position the mucous membrane is somewhat different in hue, being less pink than the fundus mucous membrane, and presents much fewer folds owing to its closer attachment to the subjacent muscular tissues.

In the dead stomach there is no *external* sign of this difference between the mucous membrane at the two ends of the stomach; but in the living stomach, or in the stomach just removed from the animal and kept in warm salt solution, the line of demarcation between the two types of mucous membrane is marked externally by a deep furrow, often spoken of as the 'transverse band.' In many cases, the whole segment of the stomach between this transverse band and the pyloric orifice is contracted to form a tube, which looks as if it were a direct continuation upwards of the intestinal tube. There is a marked difference between the movements carried out by the two portions of the stomach. The cardiac end and fundus represent a sort of reservoir, which is distended by, and slowly contracts upon, the mass of food, driving all its fluid portions towards the pyloric end. In the pyloric fifth of the stomach there is a continual series of waves of contraction, which pass from near the transverse band to the pylorus and provide for a thorough admixture of the fluid parts of the food with the secreted gastric juice, finally expelling the semi-digested chyme through the pyloric orifice into the duodenum. Although both parts of the stomach are beset with tubular glands, there are important differences in the structure of the glands in the two parts. In man and dog the tubular glands in the fundus present a neck or duct which is lined with simple columnar cells and forms one-third of the whole gland. Into this duct open one or two secreting tubules, which are lined by epithelial cells of two kinds, namely, the central or peptic cells, and large oval cells lying between them and the basement membrane, the parietal or oxyntic cells. At the pyloric end the ducts form from one-half to two-thirds of the glands and divide into three or four secreting tubules. The latter present only one kind of cell, which is similar to the peptic or central cell in the fundus

glands. Since it has been found that the secretion of the fundus glands contains hydrochloric acid as well as the proteolytic ferment, pepsin, whereas that obtained from the pyloric glands contains no free hydrochloric acid, but only pepsin, it has been concluded that the parietal cells secrete the acid, while the central cells in both types of gland secrete the pepsin. The changes in the latter cells, which accompany activity, are exactly analogous to those we have already studied in the salivary glands, the resting cells being loaded with granules which are discharged during activity.

In order to determine the characters of gastric juice, we must have some method at our command of obtaining it in sufficient quantity, free from admixture with food substances, or other secretions such as saliva. In the case of the stomach we cannot connect a cannula with a main duct and so lead away the secretion obtained during a meal. We must therefore take the secretion which is poured into the whole cavity of the stomach, and adopt some method which, while retaining the normal stimulus of a meal, will prevent the entry of food into the stomach or into that portion which we use for our experiment.

It is comparatively easy in dogs to establish a fistulous opening into the stomach, and so collect any juice which is poured out in this viscus. In such animals it is found to be impossible to evoke secretion into the stomach by mechanical excitation of its internal surface, whereas it is only necessary to show the dog food, or allow it to begin the mastication of food, in order to produce a flow of gastric juice. In order to collect the juice poured out under such circumstances, free from admixture with food or saliva, Pawlow has adopted the method of dividing the œsophagus in the neck and bringing the two ends to the surface. At the same time a fistulous

opening is established through the abdominal wall into the stomach. Such animals can be fed by the introduction of fluid food through the lower cut end of the œsophagus, or directly through the fistulous opening into the stomach. They can also take a meal in the ordinary way, but the food which is swallowed will always fall out of the opening of the

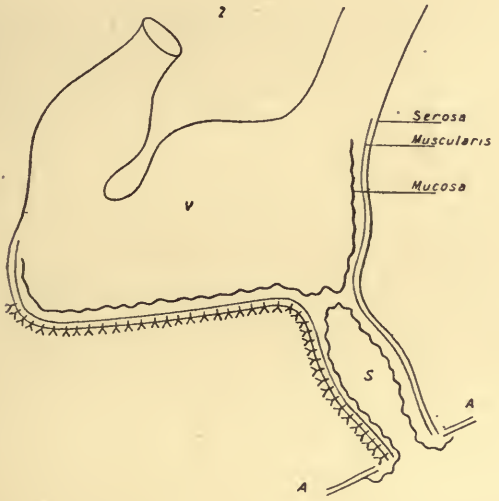

FIG. 6.—Diagram showing the manner in which the stomach is divided into two cavities, separated only by a diaphragm of mucous membrane, and still in muscular and nervous continuity. *V.* Cavity of main stomach. *S.* Small or sample stomach opening on to exterior. *A.-A.* Abdominal wall.

œsophagus on the surface of the neck, none of it reaching the stomach. Pawlow has shown that if such an animal be given food, when hungry, it will eat with avidity, and since the food cannot reach the stomach and so satisfy its hunger, it will continue to eat for two or three hours. Five minutes after the beginning of this sham feeding, gastric juice begins to drop from the fistulous opening; and in this way large

quantities of juice, free from any admixture with other substances, can be easily obtained.

By this means we obtain a secretion of gastric juice, which is excited by the presence of food in the mouth. This method does not, however, enable us to determine whether the character of the juice will be altered in any way by the changes which the food undergoes in the stomach itself. In order to form an idea of the normal course of secretion of gastric juice, when food is taken into the stomach in the ordinary way, Pawlow has devised another procedure. A small diverticulum representing about $\frac{1}{10}$ of the whole stomach is made at the cardiac or pyloric end, in direct muscular and nervous continuity with the rest of the stomach, but shut off from the main part of the viscus by a diaphragm of mucous membrane. The method in which this operation is carried out will be evident by reference to the diagram (Fig. 6). In a dog treated in this way it is found that the amount of juice secreted by the small stomach always bears the same ratio to the amount secreted by the large stomach, while the digestive power of the juice obtained from the small stomach is equal to that obtained from the large. This is shown in the following table.*

In this case a fistulous opening had been established into the large stomach, so that the juice could be obtained simultaneously from both sections of this organ. Secretion was excited by a sham meal, in which the food taken by the animal dropped out of an opening in the neck, and was not allowed to reach the stomach. It will be seen that the secretions in the two sections of the stomach run parallel to one another, while there is an almost exact equivalence

* Pawlow, "The Work of the Digestive Glands" (translated by W. H. Thompson, M.D.), p. 80.

between the strengths of the juices obtained from each section. We may therefore regard the secretion obtained from the small stomach as a sample of that produced by the large, and from the changes in this small stomach judge of the effects occurring in the whole organ. By this method it is possible to study the effects of a normal meal in which the food is swallowed, or of a sham meal in which the food is merely masticated in the mouth, or of a meal in which the food is directly introduced into an opening into the large stomach.

SECRETION FROM GASTRIC FISTULÆ AFTER SHAM MEAL.

Hours.	Small Stomach.		Large Stomach.	
	Quantity.	Strength.*	Quantity.	Strength.
1	7·6 cc.	5·88 mm.	68·25 cc.	5·5 mm.
2	4·7 cc.	5·75 mm.	41·5 cc.	5·5 mm.
3	1·1 cc.	5·5 mm.	14·0 cc.	5·38 mm.
Total ..	13·4 cc.	—	123·75 cc.	—

The gastric juice obtained in any one of these ways is a clear colourless fluid like water, containing from 0·3 to 1 per cent. total solids, and having an acidity equivalent to 0·48 per cent. hydrochloric acid. If obtained from the fundus, and therefore acid in reaction, it has a strong digestive action on proteids. If allowed to act on proteids for prolonged periods, it converts a large proportion of these bodies into amino-acids and other products. In the course of a digestion

* The strength of the juice was determined by measuring the number of millimetres of coagulated egg white (in Mett's tubes) which were digested in eight hours.

extending over three to six hours, *i.e.*, the time usually occupied by gastric digestion, the greater part of the proteid is converted only into its first products of hydration, namely, albumoses and peptones, and it is in this condition that the proteids of the food are normally passed on into the first section of the small gut. This action of the gastric juice on proteids must be ascribed to the presence in the juice of a ferment, pepsin, acting in conjunction with free hydrochloric acid. If the collected juice be placed in an ice chest for twenty-four hours, it will become turbid from the production of a finely granular precipitate. The precipitate gradually sinks to the bottom, and probably represents pepsin in the purest form in which it is possible to obtain it. That pepsin forms an unstable compound with the hydrochloric acid is shown by the fact that, if two portions of the cooled fluid be taken, one from the clear layer near the top of the vessel and the other from the turbid suspension at the bottom, the latter, which contains the greater part of the pepsin, contains also a larger percentage of hydrochloric acid than the top layer. If the hydrochloric acid were absolutely free in the solution, its distribution throughout the fluid would be the same.

We must now inquire into the conditions which determine the secretion of the gastric juice. The method, which we must adopt for its collection, shows that we have here to do, in the first place, with a reflex nervous mechanism, since an active secretion is excited by the presence of food in the mouth and by its mastication. Moreover, a secretion, which is at least as vigorous as that produced by a sham meal, can be evoked by merely arousing in the dog the idea of a meal. In this case the secretion must be determined by events in the brain which involve the co-operation of the cerebral cortex. If the animal be hungry, it is sufficient to

show it the food to produce a secretion. In the experiment from which the following table is taken, the dog was continually excited by showing it meat during a period of an hour and a half. At the end of this time the animal, which had an œsophageal fistula, was given a sham meal. It will be observed that the psychical secretion obtained during the first period of the experiment was rather greater than the secretion produced by the introduction of food into the mouth.

PSYCHICAL SECRETION OF GASTRIC JUICE. (PAWLOW.)

Time.	Quantity.
8 minutes	10 cc.
4 ,, ...	10 ,,
4 ,, ...	10 ,,
10 ,, ...	10 ,,
10 ,, ...	10 ,,
8 ,, ...	10 ,,
8 ,, ...	10 ,,
19 ,, ...	10 ,,
19 ,, ...	8 ,,

SHAM FEEDING.

Time.	Quantity.
17 minutes	10 cc.
9 ,, ...	10 ,,
8 ,, ...	10 ,,

The afferent channels for this reflex may be therefore either the afferent nerves from the mouth, or, when the *idea* of food is involved, any of the nerves of special sense, such as sight, smell, or hearing, through which these ideas are called forth. The efferent channels can only be one of two nerves, viz :—the vagus and the sympathetic, since these are the only two which are distributed to the stomach. That it is the former of these nerves which is involved is shown by the fact, recorded by Pawlow, that psychical secretion, as well as the results of a sham meal, are entirely abolished by division of both vagi. On this account division of both vagi may give rise to entire

absence of gastric digestion, and death of the animal may ensue from inanition, or from poisoning by the products of decomposition of food in the stomach, even when care has been taken to avoid injury to the pulmonary and tracheal branches of these nerves.

The converse experiment of exciting secretion by direct stimulation of the vagus presents greater difficulties. Stimulation of the vagus in the neck causes stoppage of the heart, and consequent anæmia of the mucous membrane of the stomach. Moreover, the stomach seems to be much more susceptible than the salivary glands to the action of poisons, such as anæsthetics. Its activity is also easily affected by inhibitory impulses arising in the central nervous system as the result of either painful impressions or emotional states of the animal. In order to avoid these disturbing factors Pawlow proceeded as follows:—An animal with fistulæ of œsophagus and stomach had one vagus nerve divided. A thread was attached to the peripheral end of the cut vagus and allowed to hang out through the wound. Four days after the operation the vagus was drawn out of the wound by carefully pulling on the thread, so as not to hurt or frighten the animal in any way, and its peripheral end stimulated by means of induction shocks. No effect was produced on the heart, owing to the degeneration of the cardio-inhibitory fibres, which is well known to occur within this period after section. Five minutes after the commencement of the stimulation, the first drop of gastric juice appeared from the gastric cannula, and a steady secretion of juice was obtained with continuation of the stimulation. This experiment furnishes the decisive and final evidence that the secretory nerves to the stomach run in the two vagi. There is one marked difference, however, between the action of these nerves and the action of the chorda tympani nerve on the submaxillary gland, namely,

the great length of the latent period before gastric secretion occurs. The length of this latent period has not yet been satisfactorily explained. It cannot be due to delay occurring between the vagus fibres and the local nervous mechanism in the stomach. It may be that the chemical changes finally resulting in secretion require a longer period for their accomplishment than is the case in the salivary gland. Physiologically there is, indeed, no special need for a rapid secretion of gastric juice, whereas in the mouth it is essential that the introduction of food should be immediately followed by the production of saliva, for the tasting and testing of the food and for its subsequent mastication or rejection. Another possible explanation of this prolonged latent period we shall have to consider later.

These experiments show conclusively that an important—probably the most important—part of the gastric secretion is determined by a nervous mechanism. This nervous secretion does not, however, account for the whole of the gastric juice obtained as the result of a meal. If an animal provided with two gastric fistulæ, one into a diverticulum and the other into the main stomach, have both its vagi divided, it is found that the introduction of meat into the large stomach is followed, after a period of twenty to forty-five minutes, by the appearance of a secretion of gastric juice from the small stomach. Moreover, when an animal is given a normal meal, and is allowed to swallow the food after mastication, the total amount of gastric juice obtained is greater than that produced by the sham feeding alone, and the flow is of longer duration. In fact, we may say that the gastric juice secreted in response to a normal meal consists of two parts, viz., (1) a large amount, the secretion of which begins within five minutes of the taking of the food and is determined by the reflex nervous mechanism described above; and (2) a smaller portion, the secretion of

which is excited by the presence of the food in the stomach. This combined character of the gastric juice produced by a normal meal is shown in the following table:*

SECRETION OF GASTRIC JUICE.

Hours.	Normal meal. 200 gr. meat into stomach.		150 gr. meat into stomach.		Sham meal.		Sum of two last experiments.
	Quantity. cc.	Strength. mm. dig.	Quantity. cc.	Strength. mm. dig.	Quantity. cc.	Strength. mm. dig.	Quantity. cc.
1 ..	12·4	5·43	5·0	2·5	7·7	6·4	12·7
2 ..	13·5	3·63	7·8	2·75	4·5	5·3	12·3
3 ..	7·5	3·5	6·4	3·75	0·6	5·75	7·0
4 ..	4·2	3·12	5·0	3·75	0	0	5·0

In the first column is given the result of a normal meal on the secretion from the gastric diverticulum. In the second column is given the amount and digestive power of the juice which is excited by the direct introduction of 150 grs. of meat into the large stomach of the animal, care being taken not to excite in any way the nervous reflex mechanism. In the third column is given the amount and digestive power of the juice which is evoked by a sham meal of 200 grs. of meat. In the fourth column is given the sum of the last two experiments. It will be seen that the total effect of the sham meal *plus* the direct introduction of meat into the stomach is almost identical with the secretion obtained when the food is taken in a normal way and allowed to pass through the œsophagus into the stomach.

The second phase of the gastric secretion cannot be ascribed

* Pawlow, *loc. cit.*, p. 82.

to the intervention of the reflex vagal mechanism. Since it occurs after cutting off the stomach from its connections with the central nervous system, it must have its causation in the gastric walls themselves. That it cannot be due to mechanical stimulation is shown by the fact, previously mentioned, that it is impossible by local stimulation of the mucous membrane, by rubbing, or introduction of sand, or any other method, to evoke a secretion. Moreover, it is not produced by all sorts of food. The introduction of white of egg, of starch, or of bread into the stomach causes no secretion. On the other hand, if bread be mixed with gastric juice and allowed to digest for some time, the introduction of the semi-digested mixture into the stomach evokes a secretion. We have already seen that meat produces a secretion; still more potent than meat, however, is a decoction of meat, or bouillon, or Liebig's extract of meat, or certain preparations of peptone. Pure albumoses and peptones have no effect, so that the exciting mechanism must be some chemical substances present in meat, and produced in various other foods under the action of the first gastric juice secreted in response to nervous stimuli. Popielski has shown that this secretion occurs after complete severance of the stomach from the central nervous system, as well as after destruction of the sympathetic nervous plexuses of the abdomen. Since the injection of bouillon directly into the circulation has no effect, this author concludes that the second phase of secretion is determined by the stimulation of the local nerve plexus, and that we have here, in short, a peripheral reflex action, the centres of which are situated in the walls of the stomach itself. There is, however, one possible explanation for this second phase of secretion which was not sufficiently considered either by Pawlow or by Popielski. Although the peptogenic substances, those substances which evoke gastric secretion

on introduction into the stomach, have no effect on the gastric glands when injected directly into the blood stream, it is possible that they may have an influence on the cells which line the cavity of the stomach, and that they may produce, in these cells, some other substance which is absorbed into the blood, and acts as a specific excitant of the gastric glands. A process of this nature is known to occur in the next segment of the alimentary canal, viz., the duodenum, where it determines the secretion of the pancreatic juice and the bile.

Edkins* has carried out a series of experiments to determine whether such a chemical mechanism may not also account for the secretion of gastric juice, which is excited by the introduction of substances into the stomach. Edkins' experiments were carried out in the following way. The animal, dog or cat, having been anæsthetised, the abdominal cavity was opened, and a ligature passed round the lower end of the œsophagus so as to occlude the cardiac orifice and effectually crush the two vagus nerves. A glass tube was then introduced through an opening in the abdomen into the pyloric part of the stomach, and fixed in this position by a ligature tied tightly round the pylorus. The glass tube was connected by means of a rubber tube with a reservoir containing normal salt solution at the temperature of the body. By means of this reservoir, a certain amount of fluid was introduced into the stomach and kept here at a constant pressure; the quantity of fluid introduced varied from 30 to 50 cc. It has been shown by Edkins, as well as by von Mering, that no absorption of water or saline fluid occurs in the stomach. It is, therefore, possible to recover the whole of the fluid an hour after it has been introduced, by simply lowering the reservoir below the level of the animal's body. If secretion

* *Journ. of Physiol*, Vol. XXXIV., p. 133, 1906.

of gastric juice has occurred into the cavity of the stomach, the fluid will be increased in amount, and will contain hydrochloric acid as well as pepsin. In a series of control observations, Edkins showed that the mere introduction of this fluid into the stomach caused no secretion of gastric juice, the fluid removed at the end of an hour having the same bulk and the same neutral reaction as the fluid which had been injected. Edkins then tried the influence of injecting substances into the blood stream. The injection of peptone, of acid, of broth, or of dextrin into the blood stream produced no secretion of gastric juice. If, however, in the course of the hour during which the fluid was allowed to remain in the stomach, a decoction made by boiling pyloric mucous membrane with acid, or with water, or with peptone, was introduced in small quantities every ten minutes into the jugular vein, the fluid removed at the end of the hour was found to be distinctly acid in its reaction and to possess proteolytic properties. The injection of these substances had therefore caused the secretion of a certain amount of gastric juice containing both hydrochloric acid and pepsin. In order to produce this positive effect, it was necessary to employ pyloric mucous membrane, extracts made by infusing or boiling cardiac mucous membrane with any of these substances being without effect. Edkins concludes therefore that the secondary secretion of gastric juice is determined, not, as Pawlow and Popielski imagined, by a local stimulation of the reflex nervous apparatus in the gastric wall, but by a chemical mechanism. The first products of digestion act on the pyloric mucous membrane, and produce in this membrane a substance which is absorbed into the blood stream, and carried to all the glands of the stomach, where it acts as a specific excitant of their secretory activity. This substance may be called the gastric *secretin* or gastric *hormone*. It is

noteworthy that it is produced in that portion of the stomach where the process of absorption is most pronounced.

The normal gastric secretion is therefore due to the co-operation of two factors. The first and most important is the nervous secretion, determined through the vagus nerves by stimulation of the mucous membrane of the mouth, or by the arousing of appetite in the higher parts of the brain. The second factor, which provides for the continued secretion of gastric juice long after the mental effects of a meal have disappeared, is chemical, and depends on the production in the pyloric mucous membrane of a specific substance or hormone, which acts as a chemical messenger to all parts of the stomach, being absorbed into the blood and thence exciting the activity of the various secreting cells in the gastric glands.

It is still a moot point whether this gastric hormone is formed only in the pyloric mucous membrane, or whether it may not be also produced in the lower sections of the gut. Popielski has stated that the introduction of bouillon into the small intestine excites a secretion of gastric juice in animals, even after extirpation of the abdominal sympathetic plexuses and division of both vagi. On the other hand, introduction of the same substance into the large intestine has no influence on gastric secretion. Popielski ascribes this secretion again to a local reflex; but it is more probable that the mechanism in this case is the same as that involved in the secretion which is excited by the presence of semi-digested food in the stomach itself.

Pawlow has shown that the second phase of the gastric secretion is largely influenced by the character of the contents of the stomach. Thus the ingestion of large quantities of oil diminishes considerably the amount of gastric juice secreted, and Pawlow has suggested the administration of oil or oily

foods as a possible remedy in cases where the production of gastric juice, and especially of hydrochloric acid, is in excess. It has long been imagined that the secretion of gastric juice was stimulated by the taking of alkalies. This idea has been shown by Pawlow to be erroneous. Whereas the formation of gastric juice is increased by the administration of acids, especially after a meal, it is largely diminished by the administration of alkalies such as sodium bicarbonate. In fact, sodium bicarbonate diminishes the activity of the digestive glands throughout the alimentary tract, and can be used as a means of diminishing the secretion of gastric juice as well as the secretion of pancreatic juice.

A further important question has been propounded by Pawlow; namely, whether there is any alteration in the constitution and amount of gastric juice with variations in the character of the food. So far as concerns the first phase of secretion, the psychical or 'appetite' juice, this observer has shown that, whatever the previous diet of the animal, this juice always has the same characters, the same digestive power, and the same percentage of hydrochloric acid. He finds however that in the case of the second, or what we may call 'chemical' secretion, *i.e.* that produced by local changes in the stomach, there is considerable variation in the nature of the juice. In the following table are shown the relative effects of meat and of milk, when introduced into the large stomach, in determining a flow of juice from the small stomach of an animal with a Pawlow fistula. Whereas the secretion of juice is greatest in amount with the meat, the digestive power of the juice is greatest with the bread, and Pawlow regards these differences in the juice as determined by the variations in the stimulus applied to the gastric mucous membrane. It is doubtful however whether these results justify us in ascribing a number of specific sensibilities to the gastric mucous membrane. We

have seen that the psychical juice depends merely on appetite, and therefore will be greater in amount the more welcome the food is to the animal. On the other hand, the juice secreted in the second phase must vary according to the quantity of gastric hormone produced in the pyloric mucous membrane, and therefore with the nature and amount of the substances produced in the preliminary digestion of the gastric contents by means of

Hours.	Gastric secretion after 100 grs. meat. Two experiments.	Hours.	Gastric secretion after 600 cc. milk. Two experiments.
	Quantity of juice.		Quantity of juice.
1 ..	11·2 .. 12·6	1 ..	8·75 .. 8·25
2 ..	8·2 .. 8·0	2 ..	7·5 .. 6·0
3 ..	4·0 .. 2·2	3 ..	22·5 .. 23·0
4 ..	1·9 .. 1·1	4 ..	9·0 .. 6·25
5 ..	0·1 .. a drop	5 ..	2·0 .. 1·5
Total	25·4 .. 23·9	Total	49·75 .. 45·0

the psychic juice. The amount of juice may vary also with the salts contained in the food, according to their alkaline or acid character, and the percentage of pepsin in the juice may vary with the intensity of stimulus as well as with the quantity of fluid available for the formation of the gastric juice. These factors will co-operate in determining the characters of the whole juice secreted after any given meal, and it seems possible to explain the variations, observed on such different diets as meat and bread, without having recourse to the difficult assumption of a specific sensibility of the gastric mucous membrane to such inert substances as starch, dextrin, or egg albumen.

The second phase of secretion will continue so long as there are substances present in the stomach to act upon the pyloric mucous membrane. As the food is gradually digested, and transformed from a semi-solid into a soluble condition, the fluid portions are squeezed into the pyloric end. Here a series of waves of contraction are slowly passing from the transverse band towards the pylorus. As these waves arrive at the pyloric orifice, the sphincter surrounding this orifice relaxes for a short time, and a portion of the fluid is squirted into the first part of the duodenum. The arrival of the acid chyme in the duodenum sets up a local nervous reflex which causes contraction of the pylorus, and this orifice remains closed until, by the operation of the process which we shall study in the next lecture, the acid chyme in the duodenum is neutralised by the pouring out into the gut of alkaline digestive juices. Digestion in the stomach will therefore continue until the whole of the gastric contents are reduced to a fluid condition, and have been passed by the contractions of this viscus into the small intestine; the pylorus, towards the end of digestion, relaxing so as to allow the passage of even solid indigestible morsels of food into the duodenum.

LECTURE V.

PANCREATIC SECRETION.

The fluid chyme on entering the duodenum, the first part of the small intestine, is subject at once to the influence of the secretions of three different sets of glands, namely: (1) The intestinal glands, including those characteristic of the duodenum named Brunner's glands; (2) The pancreas; (3) The liver. The ducts of the two latter in many animals have a common opening into the duodenum, and in every case there is a co-operation between all three juices for the production of the intestinal digestive fluid. In discussing the mechanism of secretion of these juices, it will be more convenient to take each kind of gland separately.

The pancreas resembles the salivary glands, in that it is composed of a mass of tubules, which pour their secretions into a common duct opening into the duodenum. It is therefore easy to establish a temporary pancreatic fistula, by isolating the duct just before it joins the intestine, and inserting a small tube or cannula into it. A permanent fistula of the pancreas can be also established without difficulty. Indeed this operation is one of the earliest in the history of experimental physiology. De Graaf in his paper "De Succo pancreatico," published in 1677, describes a method for the formation of a pancreatic fistula, and gives a figure of an animal in which both salivary and pancreatic fistulæ had been established. The juice in each case was collected in small glass vessels tied to the tubes which had been

introduced into the ducts (Fig. 7). Claude Bernard employed a method resembling very closely that of de Graaf. Instead however of opening the intestine as in the procedure of the latter, he inserted a small metal cannula into the duct outside the intestine and secured the cannula in the abdominal wound. To the outer end of the tube was tied a little rubber bag, so

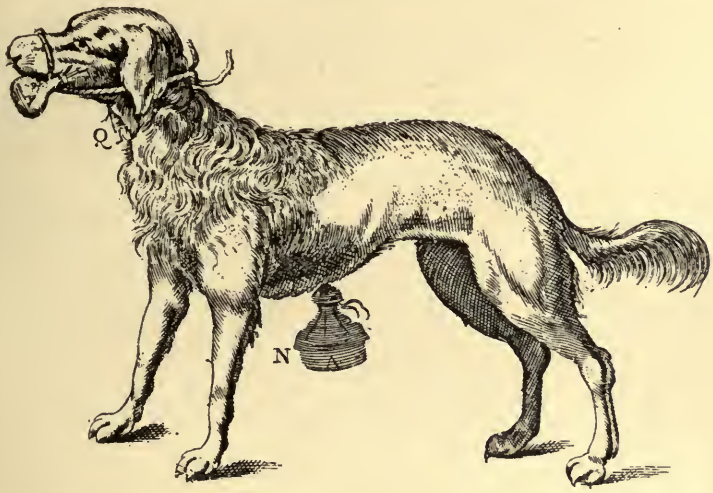

FIG. 7.—Reproduction of Plate from Réné de Graaf's treatise "De Succo pancreatico," representing a dog in which he had established both salivary and pancreatic fistulæ, small glass phials being attached to each to collect the secretions (from "Regneri de Graaf Opera Omnia." *Lugd. Batav.* 1677).

that any juice, spontaneously secreted, could be collected and drawn off at intervals for examination. The best method for the establishment of a permanent fistula is that devised by Pawlow. A small quadrilateral piece of the wall of the duodenum is excised, the position of the incision being chosen so that the papilla, with the orifice of the pancreatic duct, may lie immediately in the centre of the mucous membrane covering the excised piece. The integrity of the intestine is then restored

by suturing the margins of the wound in a direction transverse to that of the gut, and the excised piece of mucous membrane is brought to the surface and stitched into the abdominal wound. The latter rapidly heals up, so that finally the animal presents a scar on the abdomen, in the centre of which is a small pink papilla through which the pancreatic juice can escape. The juice is collected by strapping a funnel on to the belly of the dog, and connecting a flask with the lower end of the funnel. Although there are no technical difficulties in carrying out this operation, the subsequent care of the animal demands great attention. In the first place scrupulous cleanliness has to be maintained in its surroundings, in order to prevent infection of the duct with micro-organisms, which may spread up towards the gland and set up fatal pancreatitis. In the second place an animal cannot continue to lose large quantities of pancreatic juice without suffering seriously in its nutrition. Although the removal of one of the chief digestive juices from the gut may be partly responsible for this condition, the loss of the juice itself seems to be a still more serious factor. The full results of this loss can be mitigated and largely prevented by keeping the animals on a bread and milk diet, and by administration of daily doses of sodium bicarbonate. Not only does this salt replace the alkalies lost in the juice, but it lowers the total amount of the digestive juices which are secreted, including both gastric and pancreatic juices. By this treatment, therefore, the loss of pancreatic juice is reduced to a minimum.

Another troublesome feature is that the pancreatic juice, as it flows over the papilla of mucous membrane, acquires strong proteolytic properties, and tends therefore to digest the skin and other tissues in the neighbourhood of the papilla, so seriously interfering with the comfort and condition of the animal. This must be prevented in two ways. In the first place, the

proteolytic powers of the juice can be reduced to a minimum by removing the greater part of the mucous membrane surrounding the papilla. In the second place, care must be taken that, whenever the juice is not being collected, the animal is provided with a heap of sand or other absorbent material in its cage, so that the secretion may be absorbed and any moistening of the surface of the abdomen prevented.

In such an animal the normal relation of the secretion of pancreatic juice to the process of digestion can be determined. In the following table (Pawlow) the secretion of pancreatic juice resulting from a meal of 600 cc. of milk is compared with the secretion of gastric juice evoked by the ingestion of 100 gr. of meat. The gastric secretion was taken from a dog having a sample stomach, and therefore represents about $\frac{1}{10}$th of the whole gastric juice. The pancreatic secretion represents, on the other hand, the total secretion of the gland.

Gastric Secretion after a meal of 100 gms. Meat. Two Experiments.		Pancreatic Secretion after a meal of 600 cc. Milk. Two Experiments.	
Hour after Feeding.	Quantity of Juice in cc.	Hour after Feeding.	Quantity of Juice in cc.
1st ..	11·2 .. 12·6	1st ..	8·75 .. 8·25
2nd ..	8·2 .. 8·0	2nd ..	7·5 .. 6·0
3rd ..	4·0 .. 2·2	3rd ..	22·5 .. 23·0
4th ..	1·9 .. 1·1	4th ..	9·0 .. 6·25
5th ..	0·1 .. a drop.	5th ..	2·0 .. 1·5
Total	25·4 .. 23·9	Total	49·75 .. 45·0

It will be noticed that, whereas the greatest quantity of gastric juice is poured out in the first hour after the meal,

the maximum flow of pancreatic juice occurs in the third hour, at a time, that is to say, when (on this diet) the largest amount of chyme is passing from the stomach into the duodenum. There must be some causal relationship between the passage of the food through the pylorus and the secretion of pancreatic juice. It is only of late years that the nature of the connection between these two events has been brought to light. It was shown long ago by Bernard that a flow of juice could be provoked by the introduction of ether into the stomach or intestine. This, as well as the flow occurring when the acid chyme passed into the duodenum, was ascribed to the intermediation of a reflex arc; but much difficulty was experienced in the search for the channels of the reflex. Thus Heidenhain, who devoted special attention to this point, was unable to produce any secretion by stimulation of the vagus or splanchnic nerves, and though, in a few cases, some secretion was obtained on stimulation of the medulla oblongata, the results were quite inconstant. Pawlow ascribed the failure of previous experimenters to the unphysiological conditions under which their operations were carried out. Here, as in the stomach, he imagined that it was necessary to operate on an animal unpoisoned by anæsthetics, with a normal blood pressure, and free from pain or discomfort, and that the ill success of previous observers was due, either to the existence of these disturbing factors, or to the actual inhibition of the glandular activity by reflex means. When, by the employment of methods similar to those I described in the case of the stomach, Pawlow avoided the possibility of such disturbing factors, he succeeded in obtaining on stimulation of the vagus a flow of pancreatic juice. In a few cases a similar flow was obtained on stimulation of the splanchnic nerves, and Pawlow therefore regarded pancreatic secretion as determined, either reflexly or psychically through the cortex, by impulses leaving

the central nervous system and travelling to the gland along one of these two sets of nerves.

It is difficult, however, in the case of the pancreas to be certain of the existence of a real psychical secretion. There is no doubt that a flow of juice may be observed within three or four minutes of the taking of food, but it is difficult to eliminate in this case the possibility of some motor reaction of the stomach having driven a certain amount of acid juice into the beginning of the small intestine, and therefrom started reflexly a flow of pancreatic juice. The most potent method of producing a flow of juice is the introduction of acid into the duodenum or small intestine, and this method has until lately been adopted, whenever it has been desired to obtain pancreatic juice. The importance of this long reflex arc, namely from intestine to central nervous system and back along vagus or splanchnics, was later much diminished by the work of Wertheimer* of Lille, as well as of Popielski,† a pupil of Pawlow. Both these observers showed that the secretion of juice, evoked by introduction of acid into the small intestine, was absolutely unaffected by division of both vagus and splanchnics, by excision of the spinal cord, or by extirpation of the abdominal sympathetic. They therefore regarded the secretion as being due to a local reflex, started in the mucous membrane of the gut, and travelling thence to the collections of ganglion cells which are found in large numbers in the pancreas. These collections acted as reflex centres which transmitted secretory impulses directly to the cells of the pancreas.

This explanation was of considerable interest to Bayliss and myself, since we had been lately studying the local motor

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* Wertheimer, Compt. rend., cxxix. 19. p. 737, 1899.

† Popielski, Pflüger's Archiv., lxxxvi. p. 215.

reflexes of the intestine, and we therefore instituted a research with a view to determining the conditions and paths of this local secretory reflex. The research was rendered easier by the fact, discovered by Wertheimer, that the intensity of the secretion, evoked by the introduction of acid into the small intestine, diminished the further down in the gut the acid was introduced. The greatest flow was obtained when the acid was injected into the duodenum, while, if it were introduced into a loop composed of the lowest foot or two of ileum, no secretion whatever was obtained. In one experiment, therefore, we ligatured a loop of the upper part of the jejunum at two ends, and then introduced 25 cc. of ·4 per cent. H.Cl. A flow of pancreatic juice was obtained. We then proceeded to destroy all possible nervous connections between this loop and the pancreas. Both splanchnics and vagi were divided, the abdominal sympathetic ganglia round the big vessels extirpated, and all the nerve filaments travelling along the vessels to the ligatured loop were dissected away. The mesentery was divided at the same time, so that the loop of intestine was connected to the rest of the body only by its blood vessels. Acid was then introduced for a second time into the lumen of the gut (cp. Fig. 8). Although all nervous connections between gut and pancreas had been destroyed, the reaction was the same as in a normal animal, and a copious flow of pancreatic juice was obtained. This experiment proved at once that there could be here no question of a nervous reflex, either central or peripheral, but that the connection between mucous membrane and pancreas must be chemical and be effected through the blood. We knew already, from Wertheimer's researches, that the direct introduction of acid into the blood produced no flow of pancreatic juice. What was the difference between the introduction of acid into the gut, which did produce a flow, and its introduction into the blood, which did not

produce any flow? The sole difference must lie in the layer of epithelial cells, which intervene between the lumen of the gut and the capillary blood vessels in the intestinal villi. In these cells some substance must be produced under the action of acids which, on absorption into the blood, acts as the chemical messenger to the pancreatic cells. The testing of this hypothesis was very easy. The loop of intestine was cut out, the cells lining its mucous membrane scraped off and

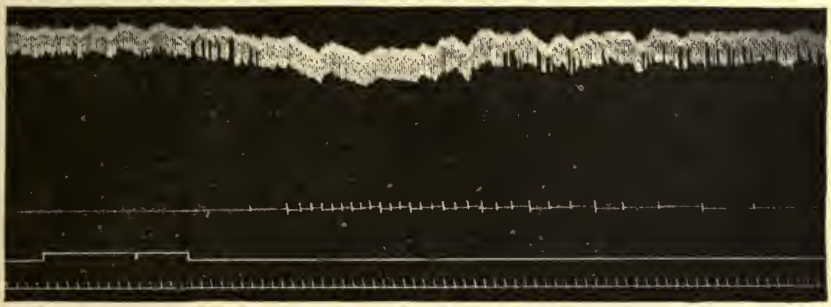

FIG. 8.—*Effect of injection of acid into loop of small intestine after destruction of its nervous connections.* Upper curve—blood pressure. Uppermost of three lines—drops of pancreatic juice secreted. Middle line—signal marking injection of 50 cc. 0·4 per cent. HCl. Lowest line—time in 10″. Blood pressure zero—level of time marker.

pounded up with some of the dilute hydrochloric acid. This extract was filtered, and the injection of the filtrate into the animal's veins was found to produce a flow of juice even greater than that excited by the introduction of acid into the lumen of the gut. This substance, formed in the cells under the influence of the acid, we have called *secretin*. It can be prepared from the upper part of the intestine of any animal belonging to the class of vertebrata by scraping off the mucous membrane, pounding it up, and boiling with dilute hydrochloric acid. When the mixture is boiling it is nearly neutralised, so as to precipitate coagulable proteids, and then

filtered. The filtrate may be introduced into the veins of any animal, and will in every case produce a flow of pancreatic juice, whether the animal be frog, bird, or mammal, and whatever be the origin of the secretin solution. We have not yet succeeded in isolating the secretin itself. The fact that it is not destroyed by boiling shows it is not a ferment. It is diffusible; it is soluble in alcohol or alcohol and ether. It is however very readily oxidised, and this fact makes it difficult to concentrate its solutions by evaporation. It is not thrown down by any of the reagents used for the precipitation of bases or proteids. Secretin may be formed from mucous membrane by the action of any acids, or even by simply boiling the tissue with water. On the other hand mere extraction with cold water or alcohol in which secretin is freely soluble, does not result in the production of an active solution. We may therefore conclude that the epithelial cells lining the gut contain a body—pro-secretin—which is insoluble in water, alcohol, or salt solution, but which, under the influence of agents such as acids, undergoes hydrolysis with the splitting off of a new body—secretin (Fig. 9). That this chemical mechanism is normally involved in the production of pancreatic secretion and is responsible for the flow obtained on the introduction of acid into the small intestine, is shown by the fact that its distribution in the gut exactly corresponds with Wertheimer's results. Thus, whereas extraction of the mucous membrane of the duodenum yields a very strong solution of secretin, a similar acid extract or decoction of the lower two feet of ileum yields a solution which has no influence on the pancreas.

We have here an example of a type of mechanism which probably plays an important part in the correlation of activities of many organs of the body. In the normal life of the higher animals, which must be considered as a continuous series of

reactions to changes in the environment, ending only with the death of the animal, those reactions, which are carried out through the intermediation of the nervous system, play such a preponderant part, that we have almost forgotten the possibility of other means of co-adaptation among the different organs of the body.

Yet, in the lowest organisms, before the appearance of any

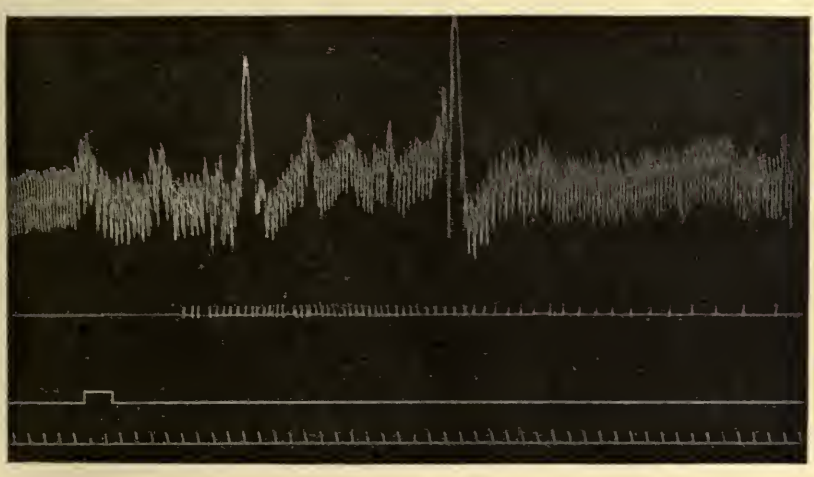

FIG. 9.—Effect of secretin prepared by the action of dilute acid on intestinal mucous membrane which had been extracted with hot absolute alcohol. The effect on the pancreas is the same as with the extract of fresh mucous membrane, but the alcohol has removed the substance responsible for the fall of blood pressure, which generally follows the injection of fresh extracts.

central nervous system, it is by chemical means that any co-ordination of function is determined, either among the different organisms of a colony, or among the various cells making up a multicellular organism such as the sponge. In this case the mechanism, which determines the movement of phagocytic cells towards an irritant, the chase of food, the escape from noxious environment, or the approach of sexual

cells, has been given the name of chemiotaxis. Since the application of these chemical stimuli depends on their diffusion through the medium bathing the cells, the process is necessarily a very slow one. So far as the communication of one cell with another in the same organism is concerned, the process could be quickened by the circulation of a common nutrient fluid such as the blood. Before the appearance of such a vascular system, however, we find that the need for quick reactions has determined the setting apart of special reactive cells, endowed with a sensibility above that of their fellows, and united with the surface and the various tissues of the body by strands of protoplasm, specially endowed with conducting powers (nerve fibres). The whole history of the evolution of the higher types of animal henceforward centres about this nervous system. It is only in respect of the complexity of his nervous reactions that man himself has any advantage over the lower animals or plants. The development, however, of a special nervous system, adapted for the carrying out of quick reactions to changes in the environment, has not abrogated the more lowly and primitive method for co-ordinating the activities of different parts of the body. Where the necessity does not exist for a specially rapid reaction, as for instance in the adaptation of the activities of the digestive glands to the presence of food in the alimentary tract, one might expect to find, as we have found, that the connection between the part of the body receiving the stimulus and the part of the body which has to react to the stimulus should be by chemical means. Of these chemical messengers or hormones, as they may be termed (from ὁρμαω, arouse or excite), we already know several examples. The hormones determining gastric and pancreatic secretion we have dealt with in these last two lectures. We shall come across evidence later on for the existence of similar bodies, which determine the secretory

activity both of the liver as well as of the intestinal glands. The suprarenal bodies manufacture in their medulla a substance—adrenalin—which, travelling over the whole body, seems to be a necessary condition for the excitation of any sympathetic nerves. In the absence of this substance there is a fall of blood pressure which is fatal within a very short time. The thyroid gland in the same way manufactures some substance, perhaps thyro-iodin, which is necessary for the proper growth of the tissues of the body and especially for the discharge of the cerebral function. The fœtus during pregnancy appears to secrete into the maternal blood some chemical substance which excites the growth of the mammary glands. It is probable that with increasing knowledge the list of these messenger substances will be largely extended and that, with their isolation, we shall have at our command means of influencing the growth and activity of the majority of the organs of the body. It is worthy of note that these substances do not belong to the group of physiologically active agents of complex and indefinite chemical composition, such as the ferments and toxins, but are in all probability well defined chemical substances, highly unstable in most cases, but capable of analysis and, in some cases at any rate, of artificial synthesis. They are comparable in many respects to the alkaloids and other substances of definite chemical composition, which form the drugs of our pharmacopœia. The practice of drugging would seem therefore to be, not an unnatural device of man, but the normal method by which a number of the ordinary physiological processes of the organism are carried out.

The question now arises whether this chemical mechanism is the only means employed in the body for the excitation of pancreatic secretion. We have seen that the action of the most effective method for procuring a flow of pancreatic juice, *i.e.*

the introduction of acid into the small intestine, is entirely due to the splitting off of secretin under the action of the acid, and have given reasons for regarding this as a hydrolytic process. There are certain substances, however, which may produce pancreatic secretion when introduced into the intestine, but do not form secretin when rubbed up with the mucous membrane. Thus a flow of juice may be obtained by the introduction, into a loop of small intestine, of oil or of irritant substances, such as ether or oil of mustard, which have no effect in producing secretin from the scraped off mucous membrane. Some light on the action of oil is thrown by the observations of Fleig, who showed that, if the mucous membrane be rubbed up with a solution of soap, the resulting mixture contains secretin, and will evoke a pancreatic secretion on introduction into the blood stream. This observer regards the secretin produced in this way as different from that produced by the action of acid, and therefore christens it 'sapocrinin;' but, apart from its mode of preparation, there is no evidence of any difference between the two. Wertheimer, moreover, has shown that if oil of mustard be introduced into a loop of intestine, and the blood from this loop be led into the veins of a second dog, a flow of pancreatic juice will occur in the latter, showing that the blood flowing from the loop contains secretin. It is possible that the action of oil may be due to the formation of a certain amount of soap as the oil comes in contact with the mucous membrane, and that this soap is responsible for the formation of the secretin. The action of oil of mustard can only be explained as a formation of secretin by a process of hydrolysis in the over-stimulated cells of the small gut, perhaps as one of the stages in the death of the cells. Whether the vagus can still be credited with any direct secretory action on the cells of the pancreas must be regarded as highly doubtful. The normal effect of stimulating the vagus is to cause

movements of the stomach, and either relaxation or contraction of the pyloric orifice. The first effect, therefore, of stimulating this nerve may be to cause a flow of the contents of the stomach into the duodenum, and the contact of the acid contents with the mucous membrane will give rise to the production of secretin and therefore set the whole chemical mechanism going. When proper precautions are taken to prevent the escape of fluid from the stomach into the duodenum, the effect on the pancreas of stimulating the vagus is so insignificant that it can hardly be regarded as evidence of the presence of secreto-motor fibres in this nerve. We see therefore that, whereas in the mouth the reaction, which must be rapid, is entirely nervous, in the stomach there is a mixture of the nervous mechanism with the more primitive chemical mechanism. The nervous secretion preponderates in this viscus. When we come to the pancreas, the primitive chemical mechanism, namely the formation of hormones and their circulation through the blood to the reactive tissue, suffices to account for the whole activity of the gland, and it is doubtful whether in this activity the nervous system plays any part whatsoever.

LECTURE VI.

CHANGES IN THE PANCREAS DURING SECRETION.

Our study of the submaxillary gland taught us that the act of secretion involves the expenditure of energy, which has its seat in the cells lining the secretory alveoli. This expenditure of energy is necessary, not only for the formation of the specific constituents of the saliva out of the blood, but also for the separation of a fluid having a smaller molecular concentration than the plasma. In addition to this osmotic work, mechanical work must be performed in raising the pressure in the duct, if there is any hindrance to the flow of the saliva. Under these circumstances the pressure within the duct may rise to a height which is double that of the blood in the arteries supplying the gland. We concluded that this energy must be determined by the changes in the structure of the cells, which give rise to a formation of granules from the protoplasm, and later on to discharge of these granules and their conversion into the fully formed secretion.

The chemical changes, that are concerned in the transformation of the food materials supplied to the cells of the pancreas into the specific constituents of the pancreatic secretion, may also be expected to involve an expenditure of energy. In the case of the pancreas, however, there is no evidence of work done in changing the molecular concentration of fluid or in the production of a secretion pressure. If the duct be occluded, the pancreatic secretion ceases at a pressure of a few centimeters H_2O, owing no doubt to the ease with which any fluid

formed by the gland cells escapes through the alveoli into the surrounding lymph spaces. The molecular concentration of pancreatic juice, as judged by its freezing point, is almost identical with that of blood plasma.

That work is done in the process of secretion is shown by a determination of the amount of oxygen used up by the resting and by the secreting gland respectively. Experiments carried out with Dr. Barcroft have shown that the oxygen intake of the gland is approximately the same as that of the salivary gland, and that, as in the latter, the intake is increased two or three fold when the gland is made to secrete by the intravenous injection of secretin.

These experiments were carried out in the following way:—

In an anæsthetised dog the abdomen was opened, and the vein leading from the tail of the pancreas (which amounts to about one-sixth of the whole organ) was dissected out, and ligatures were so placed that a cannula might be rapidly inserted into the vein at a later stage of the operation. A cannula was placed into the pancreatic duct and the abdomen closed. The dog's blood was then rendered uncoagulable (to prevent obstruction of the cannula by clotting) either by the injection of leech extract or by bleeding the animal several times, defibrinating, and returning the blood. The abdomen was then opened, and a cannula placed in the pancreatic vein. The blood flowing from this was collected in measured vessels, (*a*) immediately; (*b*) during active secretion excited by the injection of secretin. The total flow per minute was also measured. Corresponding samples of arterial blood were taken at the same time from the carotid artery. The gases from all these samples were collected by means of a mercurial pump and analysed, and the total gaseous changes of the gland were thus determined.

When we investigate the histological changes in this gland which accompany activity, we find many analogies with the corresponding changes in the salivary glands and stomach. The pancreas, however, presents certain peculiarities which merit particular attention. The normal pancreas consists of a series of secretory tubules which branch out from small ducts, the latter leading into a few large ducts. The small

ducts are lined with a layer of narrow hyaline cells, the protoplasm of which does not stain with either basic or acid dyes. At the point where a duct becomes continuous with a secreting tubule, we find outside these hyaline cells a layer of typical secreting cells. In cross section, therefore, such an alveolus shows two layers of cells, the continuation of the duct cells in the centre being known as the centro-acinar cells. Towards the end of the alveoli the centro-acinar cells disappear, leaving only the secreting cells. The latter in an ordinary resting gland, *i.e.*, one taken from an animal which has not had food for twelve to twenty-four hours, show two well-marked zones. The outer zone consists of protoplasm with a strong affinity for basic dyes such as hæmotoxylin or toluidine blue. The inner zone, *i.e.*, that turned towards the lumen, is made up of a mass of coarse granules, closely packed together, which stain intensely with acid dyes such as eosine. The nucleus, which is round and contains one or two well-marked acidophile nucleoli, is situated in the inner part of the protoplasm or basophile zone. If the gland has been secreting, the lumen of the alveoli contains a structureless material which, like the granules, stains deeply with eosine. If we study the process of activity in the living gland of the rabbit, as was done by Kühne and Sheridan Lea, we find that secretion, such as is produced by the injection of pilocarpin, causes a diminution in the size of the cells and a discharge of the granules of the inner zone. We may conclude that here, as in the salivary glands, the act of secretion involves some change in the granules and their discharge from the cell in the form of secretion. In the pancreas, as in the submaxillary gland, the process of dissimilation, which determines the formation of a secretion, is accompanied by a process of assimilation, *i.e.*, the building up of fresh protoplasm from the surrounding lymph, and its continuous conversion into secretory granules. It is

evident that the occurrence of changes, such as I have described as the result of secretion, signifies a preponderance of the processes of dissimilation over those of assimilation, so that the whole cell gets smaller. This preponderance, however, is not a necessary feature of secretion. In the heart, for instance, the dissimilation which accompanies contraction is followed immediately or attended by an assimilation, which exactly balances the opposite process, so that the heart can continue to contract throughout the whole of natural life. The same balancing of two processes may sometimes be observed in the pancreas. Thus in some cases we may excite a copious flow of pancreatic juice by the injection of secretin. Provided that the preparation of secretin is free from any large amount of the depressor substances, with which it is usually contaminated, the injection may be repeated time after time without interfering in any way with the general condition of the animal. In such an animal, with a good blood pressure, a secretion may be produced continuously for as long as ten hours, and the pancreas at the end of this time may react as well to the injections as it did at the beginning of the experiment. If the animal be killed at the end of the experiment, the pancreas to the naked eye has the typical appearance of a resting gland. It is firm, opaque, and whitish. On microscopic examination the cells are found to possess the two zones which are distinctive of a resting gland. In this case one must conclude that the injection of this specific stimulating substance, secretin, has excited not only dissimilation but also assimilation, that it has in fact stirred up the total activities of the living cells, so that there is a copious secretion without any loss of substance to the cells themselves. Usually the effect of repeated injections of secretin is to cause a gradual poisoning of the animal by the depressor substances, which are nearly always present in the decoction of intestinal mucous membrane, and

the consequent diminution of the circulation interferes with the process of assimilation more than with that of activity or dissimilation. A similar interference can be artificially brought about if the animal be bled while the injections of secretin are being administered. In such an experiment the amount of secretion produced by each injection becomes less and less, until finally the gland ceases to respond at all. If the animal be now killed, the gland presents a greyish pink appearance and is translucent and flabby. Sections made of such a gland, and stained with toluidine blue and eosine, show a diminution in the size of the cells and a diminution or entire disappearance of the red-staining granular zone.

So far, then, the changes in the pancreas are exactly analogous to those in the salivary gland. Prolonged stimulation of the pancreatic cells, however, gives rise to changes to which we have no analogy in the other glands, changes which have been studied in detail by Dale. The pancreas has long been known to possess, in addition to the secretory alveoli and the ducts, certain structures, apparently separated from the secreting portions, which are called the 'islets of Langerhans.' These, which were first described by Langerhans in 1869, are roundish areas of tissue, varying in diameter between ·1 and ·24 mm., which consist of small polygonal cells with homogeneous cell substance and round nuclei without nucleoli. These cells take up any stain with great difficulty, and in ordinary sections can be seen under the low power as unstained areas among the deeper staining alveoli. Most observers have regarded these structures as a tissue distinct from he secreting tissue and merely imbedded in the latter.

Since the discovery by Minkowski that total extirpation of the pancreas gives rise to a fatal diabetes, this organ as a whole has been regarded as having two functions—(1) the secretion of a digestive fluid into the alimentary tract; (2) the secretion

into the surrounding lymph or blood stream of some substance which is a necessary condition for the utilisation of sugar in the body. It is evident that the secreting tubules are responsible for the production of the digestive secretion; many physiologists have therefore regarded the islets as the organs for the production of the internal secretion. No evidence exists in support of this notion. A tissue of unknown origin has been accredited with the equally unknown anti-diabetic function of the pancreas. Certain Russian observers have, however, suggested that these islets represent phases in the life history of the secreting alveoli, and that they are formed from the latter as the result of activity. This identity of origin of alveoli and islets receives support from the study of the structure of the pancreas in embryos. Laguesse describes the primitive buds, which in the sheep embryo form the pancreatic rudiment, as being of the nature of islets. These later become converted into secondary acini, which are again transformed into islets. The islets, after growth by continuous cell division, are yet again converted into a larger number of acini. Laguesse regards this process both as a method of growth and as representing an alternation between external and internal secreting (*exocrine* and *endocrine*) conditions of pancreatic tissue, and considers that the process may continue to some extent throughout life. Dale's investigations confirm the views of the Russian observers. The islets of Langerhans are not independent structures of separate origin, but are formed by certain definite changes in the arrangements and properties of the cells of the ordinary secreting tissue. This change is gradually accelerated by exhaustion of the gland by means of secretin. As a result of such exhaustion there is, in the first place, a multiplication of the number of cell islets, and finally a conversion of the greater part of the secreting alveoli into islet tissue. Under such conditions the islets no

longer form circumscribed spots scattered over the section but are spread diffusely throughout the whole gland.

The changes are of such a kind as to assimilate all the

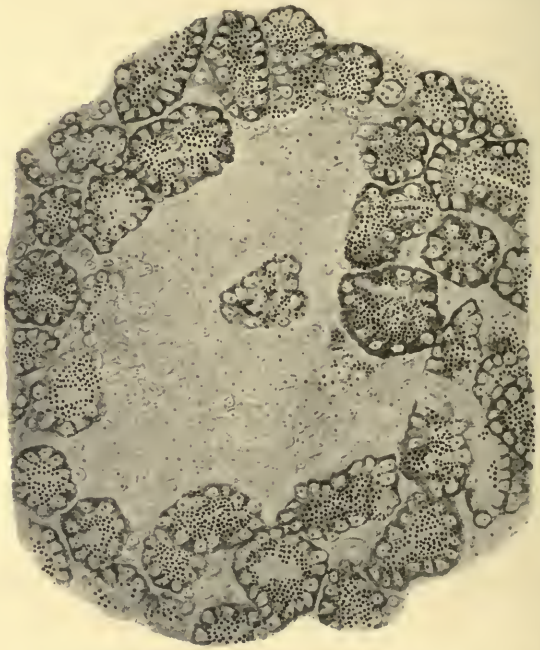

FIG. 10.—*Formation of islet of Langerhans from secretory alveoli.* Portion of the pancreas of a toad in which active secretion had been excited by the injection of secretin. The islet of Langerhans, with its unstained hyaline cells, presents a marked contrast to the secretory alveoli, with their basophile protoplasm and deeply-stained zymogen granules. The islet is, however, increasing in extent at the expense of the secreting tissue. The latter in many places is losing all its chromophile elements and undergoing conversion into islet tissue. In the middle of the islet is some of the secretory tissue where the change is not yet quite complete. (Drawn from a microphotograph of a specimen by H. H. Dale.)

cells to those forming the epithelium of the ductules and the centro-acinar cells, thus bringing about a reversion to the embryonic type. Complete exhaustion thus causes, not

only an extrusion of the whole of the secretory granules, but also an emptying out and disappearance of the whole of the basophile protoplasm. It is worthy of note that the proportion of islet tissue to secreting tissue is increased, not only by prolonged activity, but also by the prolonged inactivity which occurs during starvation. In the latter case the gland, which is not required for digestion, is called upon to give up its stored material, whether granules or protoplasm, to serve as food for the working of those parts of the body whose continuous activity is a condition of the maintenance of life —such as the central nervous system, the brain, and the respiratory muscles. In this process of wasting, the same changes are brought about in the appearance of the cells as when the discharge of their constituents is required for the production of a juice for the purpose of digestion. Since the islets are in constant process of formation from alveoli as the result of activity, there must be a constant disappearance of islets and new formation of the alveoli to maintain the balance between the tissues. The embryological evidence brought forward by Laguesse, as well as Dale's experiments on the toad, show that pancreatic growth is a function of the islets, cell multiplication being observed only in the islets which are produced as a result of extreme activity. Whether the pancreatic tissue in its islet stage has special connections with the carbohydrate metabolism of the body, or whether the anti-diabetic functions of the gland are carried out by its alveolar cells, in addition to and at the same time as their ordinary secreting functions, we are not yet in a position to state.

LECTURE VII.

THE PROPERTIES OF THE PANCREATIC JUICE.

The pancreatic juice, which is obtained after a meal from an animal with a permanent fistula, is similar in all respects to that obtained from one with a temporary fistula, as the result either of introduction of acid into the duodenum, or of the injection of secretin into the blood stream. It is a clear colourless fluid, somewhat viscid, with a specific gravity of about 1030. It contains from 2 to 3·5 per cent. total solids, of which about 1 per cent. consists of salts, the remainder of coagulable proteids. Among these proteids a certain proportion are precipitated on neutralisation. In a neutral solution about one-half the total proteids are coagulated between 55 and 60 degrees C., while the remainder are coagulated about 75 degrees C. The juice is always strongly alkaline; 10 cc. of juice for their complete neutralisation require between 10 and 15 cc. of $\frac{n}{10}$ acid. It is worthy of note that the alkalinity of the juice corresponds almost exactly to the acidity of the gastric juice. Thus in one experiment, 70 cc. of pancreatic juice, obtained by injection of secretin, required for their complete neutralisation 78 cc. of ·4 per cent. hydrochloric acid. Each portion of chyme, which is ejected from the stomach into the duodenum, will continue to excite the production of secretin in the epithelial cells until, under the influence of the absorbed secretin, the pancreas has poured out an equal quantity of pancreatic juice, and the duodenal contents are

thus neutralised. The pylorus will then open and allow a further portion of acid chyme to pass into the duodenum, to excite in the same way the secretion of a further equivalent portion of pancreatic juice. Since under normal conditions a secretion of bile occurs at the same time as the pancreatic secretion, and since bile has a certain power of neutralising the acid of the chyme, it is probable that under normal circumstances the secretion of pancreatic juice will be rather smaller in amount than the chyme passing through the pylorus. The neutralising effects of these two juices is aided moreover by the secretion of an alkaline juice by the intestinal glands. The final result will be the production of a neutral fluid in the duodenum, and it is in this neutral fluid that the processes of intestinal digestion will go on.

Pancreatic juice, obtained in either of the above-mentioned ways, contains ferments, which act as strong hydrolytic agents on starches and fats. Starch is rapidly converted by the juice into dextrin and maltose, and the maltose is more slowly transformed into glucose.* The neutral fats are split up into fatty acids and glycerin. On proteids, juice obtained from a temporary fistula has very slight action. Boiled eggwhite or gelatin are not digested even after weeks of soaking in the fluid. Fresh fibrin and caseinogen are slowly digested. The juice may therefore be said to contain a weak proteolytic ferment, resembling that which can be extracted from almost any tissue of the body. A similar ferment can be obtained from extracts of the intestinal mucous membrane, and has been named by Cohnheim *erepsin*. Its chief function in this situation appears to be the further digestion of albumoses and peptones, and their conversion into amino-acids. It seems, therefore, that the pancreatic cells, produced as an outgrowth

* The conversion into glucose takes place more rapidly in a slightly acid medium.

from the mucous membrane of the intestine, have retained the power of producing this weak proteolytic ferment in common with the other cells clothing the inner surface of the gut. These properties of fresh pancreatic juice were described by Claude Bernard, who regarded the proteolytic functions of the juice as unimportant. Corvisart however, working, not with the juice as obtained from a cannula in the pancreatic duct, but with the juice as secreted into the duodenum, described as one of its essential properties an extremely energetic action on proteids. Most of the later researchers dealt chiefly with an extract of the pancreas itself. All of these physiologists, of whom Kühne, Heidenhain, and Langley may be specially mentioned, found that the watery extract contained not only lipase and amylase, but also a substance which rapidly underwent conversion into an active proteolytic ferment. The latter was named trypsin, and its precursor in the gland trypsinogen. In the juice obtained from permanent fistulæ, Pawlow found trypsin preformed, but showed later that part, at any rate, of the trypsin was present, not in the form of ferment, but as its precursor trypsinogen. Chepowalnikow, working in Pawlow's laboratory, found that the proteolytic activity of the juice was enormously increased by adding to it a drop of intestinal juice or of an extract of intestinal mucous membrane. He therefore concluded that the juice generally contained trypsinogen, which under the influence of a ferment *enterokinase*, contained in the succus entericus, was transformed into the active ferment trypsin. Now it must be remembered that the juice obtained by Pawlow's method, before it is collected, has to trickle over the small portion of intestinal mucous membrane which is left in the abdominal wall surrounding the orifice of the duct. This mucous membrane can serve as a source of enterokinase, and Délézenne has found that, if a cannula be inserted through

the papilla into the duct, so as to prevent the juice coming in contact with the intestinal mucous membrane, the liquid so obtained contains no trypsin at all, and is without effect on coagulated proteid. We may say therefore that juice, as it is secreted normally by the pancreas, contains no trypsin, but a precursor of trypsin named trypsinogen. The trypsinogen can be converted into trypsin, only by the action of the ferment enterokinase furnished by the mucous membrane of the gut. No other agent is able to effect this transformation. The spontaneous conversion of the trypsinogen, observed by the older workers to occur in extracts of the pancreatic gland, depends, not as they thought on the acidity or reaction of the gland, but on the accidental defiling of the tissue with intestinal contents in the process of extraction from the animal. If care be taken, in cutting the pancreas out of the dead body of an animal, to avoid any contamination of the gland with intestinal contents or mucous membrane, a watery or glycerin extract, though containing trypsinogen, will remain inactive for months; but at any time it can be activated by the addition of a small amount of enterokinase.

As I have said, the discoverers of enterokinase looked upon it as a ferment which converted trypsinogen into trypsin. Since, in this case, one ferment is formed by the action of another, Pawlow spoke of enterokinase as the "ferment of ferments." More lately a different view has been put forward of the mode of interaction between these two bodies, by Délézenne, and by Dastre and Stassano,* and this view has been accepted by such authorities as Metchnikow and Ehrlich. According to them, trypsin is not a single body, but is a combination or association of two bodies, trypsinogen and enterokinase. They have thought that, just as two bodies, called the amboceptor and the complement, are involved in the

* Archives internat. de Physiol., Vol., I., p. 86, 1904.

destruction of red blood corpuscles by foreign sera, so in the destruction of the proteid molecule by trypsin, the trypsinogen serves simply to anchor the active ferment, the kinase, on to the proteid molecule. In further support of this analogy with the phenomena of hæmolysis, Délézenne has stated that enterokinase can be obtained in large quantity from lymphatic glands, as well as from the leucocytes of the blood, and is therefore simply one of the cytases, the digestive ferments contained in the phagocytic cells of the body. Such an analogy between the methods employed in the defence of an animal against invasion by foreign cells, and that employed in normal nutrition, would be of far-reaching importance, and Bayliss and I have therefore reinvestigated the question. A decision between the two views is not difficult to arrive at. If trypsin be in all cases a combination of trypsinogen and enterokinase, there must always be a certain proportion between the quantities of the two substances present in any active juice, in order that it may exert its full powers. If on the other hand enterokinase acts simply as a ferment, it does not matter how small a quantity of enterokinase is added to the inactive juice containing trypsinogen, provided that a sufficient time is allowed for the ferment to work. We have found that, as a matter of fact, the smallest trace of enterokinase is able, if it be given sufficient time, to activate any quantity of inactive juice. As we increase the amount of enterokinase added, we do not increase in any way the maximum digestive power of the juice. We simply hasten the process of activation. Moreover, if trypsin always owes its activity to an association of the two bodies, it must always contain enterokinase, and therefore be able to activate trypsinogen to which it may be added. This is not the case. Although certain preparations of trypsin contain traces of enterokinase and therefore exert a small activating effect, it is

possible to procure specimens of trypsin which have not the slightest activating influence on fresh pancreatic juice. There is a further biological test which we can apply to decide the question. Normal serum resists the digestive action of trypsin in consequence of its content in a body—antitrypsin. This antitrypsin of serum has been regarded by Dastre as an antikinase. It is possible, however, to make antikinase by injecting an animal with successive doses of enterokinase. Such an antikinasic serum differs entirely from the normal antitryptic serum. Whereas normal serum, in most cases, has no influence on enterokinase but annuls the action of trypsin, an antikinasic serum, prepared by the subcutaneous injection of enterokinase, entirely paralyses the activating power of enterokinase on trypsinogen solutions, but has no influence on the digestive powers of a solution of trypsin. Finally it has been shown by Weinland, that intestinal worms owe their immunity from digestion to a substance which is present in their tissues and which has the property of preventing pancreatic digestion. Weinland regards this body as an antitrypsin, Dastre as an antikinase. It has been shown lately by Hamill that the antibody extracted from intestinal worms acts in all respects like the antitrypsin of normal serum. It has no effect on enterokinase, and its inhibitory influence is limited to fully formed trypsin. There are no grounds therefore for the analogy which has been drawn between the interaction of these two bodies and the interaction of the two bodies which are involved in the solution of red blood corpuscles. Enterokinase is a ferment secreted by the intestinal epithelium and peculiar to this epithelium. We have found it impossible to extract any enterokinase from lymphatic glands or indeed from any tissues other than those of the intestine. There is no justification therefore for classing it with the cytases, and the results of our investigations

have been to confirm entirely the view of Pawlow, with regard to the action of this "ferment of ferments."

The Qualitative Adaptation of the Pancreatic Juice.

The mechanisms which we have studied in the last few lectures provide for a very extensive adjustment between the activity of the pancreas and the digestive needs of the animal. Substances which are difficult of digestion will remain long in the stomach and will probably excite a greater flow of gastric juice. The flow of pancreatic juice will be determined by the flow of gastric juice. The greater the amount of acid chyme entering the duodenum the larger will be the amount of pancreatic secretion. With a rapid flow we shall have a more watery juice, containing however the normal amount of sodium carbonate. The slower the flow the more concentrated in proteid and in trypsinogen shall we expect to find the juice. According to Pawlow, however, the activity of this gland shows a marvellous qualitative adaptation to the nature of the food-stuffs. His pupil, Vasilieff, found that the pancreatic juice obtained from animals with permanent fistulæ showed variations in the relative quantities of the three ferments present, according to the nature of the food, the trypsin being formed in largest amount on a diet of meat, lipase on a diet of fat, and the amylase on a diet chiefly consisting of carbohydrates. There was thus a slow accommodation of the pancreatic cells to the nature of the food which the animal receives. According to Walther the adaptation is still more rapid. If in the course of one day three meals, the first of milk, the second of bread, and the third of meat, be eaten in succession, at intervals of a few hours, the meat meal will give a juice containing the largest proportion of trypsin, while the meal of bread causes the secretion of a juice in which the

ferment amylase is preponderant. The figures obtained by this observer are given in the following tables:

Diet.	Quantity of Juice.	Proteolytic Ferment.		Amylolytic Ferment.		Fat-splitting Ferment.	
		Strength of Juice.	Total units of Ferment.	Strength of Juice.	Total units of Ferment.	Strength.	Total units.
Milk 600 cc. ..	48 cc.	22·6	1085	9	432	90·3	4334
Bread 250 gms...	151 cc.	13·1	1978	10·6	1601	5·3	800
Meat 100 gms. ..	144 cc.	10·6	1502	4·5	648	25	3600

It will be seen that, while their general statements as to trypsin and amylase are borne out by these figures, there is a very little difference between the lipase, secreted on a fatty diet such as milk, and that secreted on a proteid diet such as meat. Moreover, it must be remembered that the observations of these two physiologists were carried out before the discovery of enterokinase. The amount of trypsin they found in each specimen of juice therefore must have been purely accidental and dependent on the time at which they examined the proteolytic powers of the samples. Any postponement of the examination would give the small traces of enterokinase a longer time to act, and would increase the tryptic power of the juice. We have therefore only the results on amylase in support of the general statement as to the powers of adaptation presented by the pancreas. The subject is in need of further investigation.

Pawlow's views seemed to receive weighty confirmation from the results of an experiment conducted by Weinland. Weinland stated that, whereas the pancreas of an adult dog is free from lactase (the ferment which converts lactose into galactose and glucose), extracts made from the gland of an animal, taking milk or milk sugar with its diet,

contained this ferment. Here then was a definite example of adaptation—the appearance in the gland and presumably in the juice, of a ferment, not previously present, as the result of a special form of diet. With the view of determining the mechanism of this adaptation, Weinland's experiments were repeated by Bainbridge with the result that lactase was found in the pancreatic juice after feeding with lactose but was absent unless this substance were administered. A French observer, Bièrry, having repeated these experiments with absolutely negative results, the whole subject has been reinvestigated by Plimmer. For the purpose of determining the presence of lactase in the juice or extracts of the gland, 20 to 50 cc. of the extract or juice were allowed to digest for three days with a 5·0 per cent. solution of lactose, toluol being added to prevent bacterial changes. At the same time a control experiment was carried out, using the identical quantities, but after previously boiling the juice or pancreatic extract, to destroy any ferment that might be present. At the end of this time the proteids were removed by means of mercuric nitrate, the excess of mercury got rid of by sulphuretted hydrogen, and the amount of sugar determined in both fluids by means of Allihn's method. In this method, the copper oxide, produced by the reduction of Fehling's solution, is collected and weighed, so that no scope is left for error of judgment in determining the exact moment at which the reduction of Fehling's fluid is completed. In every case Plimmer found that the reduction power of the milk sugar, which had been treated with extracts of pancreas, or with pancreatic juice taken from animals fed for weeks on lactose, was identical with that of the control solution in which the juice or extract had been previously boiled. We must conclude, therefore, that the pancreas has no power of altering its secretion in response to the presence of lactose in the gut.

Lactase is present as a normal constituent of the intestinal mucous membrane (at any rate in young animals), so that there is no necessity for the development by the pancreas of the power of digesting this substance. The importance of Bièrry's and Plimmer's results lies in the fact, that they disprove the one definite case, in which we thought we had a qualitative adaptation of the pancreatic secretion to the nature of the food. Popielski, a former pupil of Pawlow, has himself come to the conclusion that, in the process of secretion, the pancreas pours out the whole of its contained ferments or pro-ferments, and has denied altogether the power of adaptation which has been ascribed to this gland. Pawlow regards the adaptation as determined by a specific sensibility of the mucous membrane of the duodenum to the different classes of food-stuffs and the consequent production of nerve impulses of varying qualities proceeding to the gland. We have already seen that the normal activity of the pancreas is called forth, not by nervous changes but by the chemical messenger, secretin. There is no evidence that, in the absence of this mechanism, stimulation of the mucous membrane of the intestine can evoke any pancreatic secretion, and it is therefore still more improbable that a qualitative adaptation of the juice to the type of food-stuff is determined by such a nervous mechanism. There are riddles enough in physiology without conjuring up a teleological adaptation for which the experimental evidence is inadequate, the conception of its mechanism impossible, and which is not necessary for the well-being of the animal.

LECTURE VIII.

THE BILE.

The fact that the bile, the secretion of the liver, is in so many animals poured into the intestine by an orifice common to it and the pancreatic juice, suggests that these two fluids co-operate in their actions on the ingested food-stuffs, and points to a direct use of the bile in the processes of digestion. In addition to this function, the bile must also be regarded as an excretion, representing as it does the channel by which the products of disintegration of hæmoglobin—the red colouring matter of the blood—are got rid of from the organism. As an excretion the production of bile must be continuous, and related, not to the processes of digestion, but to the intensity of destruction of the red corpuscles. On the other hand bile, as a digestive fluid, is needed in the gut only during the period that digestion is going on. The exigencies of the body, therefore, require a continuous excretion of bile by the liver, but a discontinuous entry of this fluid into the small intestine. This discontinuity in the entry of a continuous secretion into the intestine is secured, in the majority of animals, by the existence of the gall bladder, a diverticulum from the bile ducts, in which all bile, secreted during the intervals between the periods of digestive activity, is stored up. In the horse, where the gall bladder is absent, its place is taken to some extent by the great size of the bile ducts. Moreover, in such an animal the process of digestion is much more continuous in character than it is in carnivora. Since the bile accumulates in the gall

bladder during the whole time that digestion is not going on, and is only poured into the gut during digestion, we find on opening a fasting animal that the gall bladder is distended, whereas in an animal some hours after a meal the gall bladder is practically empty.

During the period that the bile secreted by the liver remains in the gall bladder, it undergoes certain changes, as is shown by comparison of the composition of bile obtained from the gall bladder with that obtained from a fistula of the bile duct.

ANALYSES OF BILE (HUMAN).

From a biliary fistula (Yeo and Herroun).		From the gall bladder (Hoppe-Seyler) in 100 parts.	
Mucin and pigments	0·148	Mucin	1·29
Sodium taurocholate	0·055	Sodium taurocholate	0·87
Sodium glycocholate	0·165	Sodium glycocholate	3·03
Cholesterin, Lecithin, Fats	0·038	Soaps	1·39
		Cholesterin	0·35
		Lecithin	0·53
		Fats	0·73
Inorganic salts	0·840		
Water	98·7		

During its stay in the bladder, the bile is concentrated by the loss of water and by the addition to it of mucin or nucleo-albumen, derived from the cells lining the bladder. Of the other constitutents of bile, the pigments must be regarded simply as waste products. They pass into the intestine and are there converted by the processes of bacterial reduction into stercobilin, which is excreted for the most part with the fæces, a small proportion being absorbed into the blood vessels and turned out in a more or less altered condition as the pigments of the urine. From the point of view of digestion, the important constituents of bile are the bile salts, with the lecithin and cholesterin held in solution by these salts. Before we enquire into the action of these essential digestive constituents, it will be interesting to determine the time

relations of the secretion, as well as of the out-pouring of bile into the intestine, in connection with the processes of digestion. These time relations can be learnt from animals in whom the bile is conducted to the outside of the body by means of a permanent fistula. In order to determine the time relations of the flow of bile into the intestine, Pawlow has devised the following operation:—In the dog, the abdomen is opened, and the common bile duct sought as it passes through the intestinal wall. The orifice of the duct, with a piece of the surrounding mucous membrane, is then cut out of the wall of the intestine, and the aperture thus made sutured. The excised portion of mucous membrane, with the opening of the duct, is then sewn on to the surface of the duodenum, and the loop of duodenum at this point is stitched into the abdominal wound. After healing, the natural orifice of the bile duct is thus made to open on the surface of the abdomen.

In an animal treated in this way, the flow of bile from the fistula is found to run absolutely parallel to the pancreatic secretion. Although smaller in amount, it rises and falls with the latter. Thus a meal of meat produces a large flow of bile, a meal of carbohydrates only a small flow. Moreover, beginning almost immediately after taking food, it attains its maximum with the pancreatic juice in the third hour, and then rapidly declines.

In the production of this flow of bile, two factors may be involved: (1) the emptying of the gall bladder; (2) an increased secretion of the bile. In order to determine the relative importance to be ascribed to each factor, we must compare the results obtained on an animal possessing a Pawlow fistula with those obtained on an animal provided with a fistulous opening into the gall bladder, the common bile duct in the latter having been ligatured to insure that the total secretion of

bile passes out by the fistula. In such animals we find, as we should expect, that the secretion of bile is a continuous process, but that, synchronously with the great outpouring of bile into the intestine during the third hour after a meal, there is an increased secretion of this fluid. The passage, therefore, of the semi-digested food from the stomach into the duodenum causes, not only a slow contraction and emptying of the gall bladder, but also an increased secretion of bile by the liver. What is the mechanism involved in the production of these two effects? The muscular wall of the gall bladder, as has been shown by Dale, is under the control of nerves derived both from the vagus and from the sympathetic, the former conveying motor and the latter inhibitory impulses. It is usual to suppose that the entry of acid chyme into the duodenum provokes reflexly the contraction of the gall bladder, but the exact paths and steps in this reflex act have not yet been fully determined. The increased *secretion* of bile, which is produced by the passage of the acid chyme through the pylorus, can be also evoked by the introduction of acid, such as ·4 per cent. H.Cl., into the duodenum, and occurs even after division of all connection between the liver and the central nervous system. Since the presence of bile is necessary for the full development of the activities of the pancreatic juice, and its secretion is initiated by the same sort of stimulus, *i.e.*, acid applied to the mucous membrane of the gut, the question naturally arises whether the mechanism for the secretion of bile may not be identical with that for the secretion of pancreatic juice. In order to decide this point we must make a temporary biliary fistula, by inserting a cannula into the hepatic duct. A solution of secretin is then prepared from an animal's intestine. In making this solution, we must be careful to avoid any contamination by bile salts, which may possibly be adherent to the mucous membrane of the

gut and would in themselves, on injection, evoke an increased secretion of bile. It is therefore better to extract the pounded mucous membrane with boiling absolute alcohol, until this fluid, evaporated into a small bulk, shows no trace of bile salts. The dried and powdered gut is then boiled with dilute acid. On injecting the solution of secretin so obtained into the animal's veins, an increased flow of bile is at once produced. In one experiment, for instance, we found that the injection into the veins of 5 cc. of a solution of secretin, prepared in this way, increased the secretion of bile by the liver from twenty-seven drops in fifteen minutes to fifty-four drops in fifteen minutes (Fig. 11). The rate of secretion was therefore doubled. We must conclude from these experiments that the mechanism, by which the increased secretion of bile is produced at the time when this fluid is required in the intestine, is identical with that for the secretion of pancreatic juice, and that in each case one and the same substance—secretin—is formed by the action of the acid on the cells of the mucous membrane, and that this secretin, on absorption into the blood stream, excites both the liver and pancreas to increased activity.

THE DIGESTIVE FUNCTIONS OF THE BILE.

Bile contains a weak amylolytic ferment. Its uses in digestion are dependent however, not on the presence of this ferment, but on the peculiar action of the bile salts on the fermentative powers of the pancreatic juice. It was shown long ago by Williams and Martin * that the amylolytic power of pancreatic extracts is doubled by the addition of bile or of bile salts. Pawlow has stated that the same holds good of the proteolytic power of this juice. Most important, however, is the part played by the bile in the digestion and absorption

* Proc. Roy. Soc., Vol. XLV., p. 48 and Vol. XLVIII., p. 160, 1890.

of fats. The fat-splitting action of pancreatic juice is trebled by the addition of bile, whether boiled or unboiled. This quickening action of the bile probably depends, like its function in the absorption of fats, on the peculiar physical properties of the bile salts, with those of the lecithin and cholesterin, which are held in solution. Not only does such a solution diminish the surface tension between watery and oily fluids, so promoting the closer approach by the lipase of the pancreatic juice to the fats on which it is to act, but it has also the

FIG. 11.—Effect of injection of secretin on the flow of pancreatic juice and of bile. The lines from above downwards represent—(1) Blood pressure; (2) drops of pancreatic juice; (3) drops of bile; (4) signal marking moment of injection of secretin; (5) time-marking 10″ intervals.

power of dissolving fatty acids and soaps, including even the insoluble calcium and magnesium soaps. It is probable that it aids also in holding in solution, and bringing in contact with the fat, the lipase of the pancreatic juice. It has been shown by Nicloux* that the lipase contained in oily seeds, such as those of the castor plant, is insoluble in water but soluble in fatty media. The dried ferment obtained from the pancreas in many cases yields no lipase to water, but gives a strongly lipolytic solution when extracted with glycerin. The digestive function of bile therefore lies in its power of serving as a vehicle for the suspension and solution of the interacting

* *V.* Proc. Roy. Soc., Series B, Vol. LXXVII., p 454.

fats, fatty acids, and fat-splitting ferment. This vehicular function plays an important part in the absorption of fats. These pass through the striated basilar membrane bounding the intestinal side of the epithelium, not, as has been formerly thought, in a fine state of suspension (an emulsion), but dissolved in the bile in the form of fatty acids or soaps and glycerin. On the arrival of these products of digestion in the epithelial cells, a process of resynthesis is set up. Droplets of neutral fat make their appearance in the cells, whence they are passed gradually into the central lacteal villus and so into the lymphatics of the mesentery and into the thoracic duct. The bile salts thus released from their function as carriers are absorbed by the blood circulating through the capillaries of the villi, and carried by the portal vein to the liver. Arrived here they are once more taken up by the liver cells and turned out into the bile. Owing to the fact of their ready excretion by the liver cells, bile salts are the most reliable cholalogues with which we are acquainted. By this circulation of bile between liver and intestine, the synthetic work of the liver in the production of the bile salts is reduced to a minimum, and it has only to replace such of the bile salts as undergo destruction in the alimentary canal, under the influence of micro-organisms, and are lost to the organism by passing out in the fæces as a gummy amorphous substance, known as dyslysin. Further investigation is still wanted as to the exact method in which secretin acts on the liver cells, and especially as to whether it actually excites in them the manufacture of fresh bile salts, or whether it simply hastens the excretion of such bile salts as have been formed by the spontaneous activity of the liver cells or have arrived at them after absorption from the alimentary canal. Such questions can only be decided by studying the action of secretin on animals possessing a permanent biliary fistula.

From the fact that the secretion of bile runs parallel with that of pancreatic juice, and is excited by the same mechanism, we should expect it to alter with variations in the diet. The secretion of bile on various diets has been studied by Barbera. He finds that, whereas the secretion of bile is greatest on a meat diet, it is somewhat less on a diet of fat, and is insignificant on a purely carbohydrate diet. That is to say, the secretion of bile is greatest on those diets, the digestion of which is attended by the passage of a large amount of acid chyme or of oil into the duodenum. We have seen earlier that oil is almost as efficacious as acid in promoting the production of secretin in the living duodenum, the production in this case being probably determined by the formation of soap from the oil, and the direct action of the soap on the prosecretin in the epithelial cells of the gut.

LECTURE IX.

THE INTESTINAL JUICE.

We have seen that for the development of one of its most important properties, namely, that of proteolysis, the pancreatic juice is dependent on the co-operation of the intestinal juice or succus entericus. Besides this activating power on the pancreatic juice, the intestinal juice has numerous other functions to discharge in the digestion of the food-stuffs. Before discussing its actions in detail, we may consider the conditions which determine its secretion. In spite of the great similarity which obtains between the microscopic structure of the wall of the gut at different levels from duodenum to ileo-colic valve, functionally there are many differences between the upper, middle, and lower portions of the gut. Speaking generally, we may say that, whereas the processes of secretion are best marked in the upper portions of the gut, the processes of absorption predominate in the lower sections, *i.e.*, in the ileum. Much of the divergence in the statements, which have been made with regard to the factors determining secretion and absorption in the small intestine, is due to the failure to appreciate this great difference between the activity of the mucous membrane at various levels. The processes of secretion in the small intestine may be studied by isolating loops by means of ligatures, and determining the amount of secretion formed in these loops in the course of a few hours' experiment on an anæsthetised animal. Better results, however, may be obtained by establishing permanent fistulæ. These fistulæ are

of two kinds. Thiry's original method of establishing a fistula consisted in cutting out a loop of intestine, and restoring the continuity of the gut by suturing the two ends from which the loop had been severed. The upper end of the loop itself is closed and the lower end is sutured into the abdominal wound. For some purposes it is better to make a Thiry-Vella fistula. In this case the continuity of the gut is restored as in the simple Thiry fistula, but both ends of the excised loop are left open and brought into the abdominal wound. In such a fistula it is easy to introduce substances into the upper end and determine the flow of juice from the lower end, the constant emptying of the loop being provided for by the peristaltic contractions of its muscular coat.

In animals with intestinal fistulæ, a number of different conditions have been found to give rise to a flow of succus entericus, and so far no qualitative difference has been recorded between the upper and lower ends of the gut. A condition, which will cause a free flow of juice from a fistula high up in the intestine, will generally cause a scanty flow from a fistula made from the ileum. In all cases it is found that a flow of juice is produced in consequence of a meal. If a dog with a fistula, which has been starved for twenty-four hours, be given a meal of meat, a flow of juice may begin within the next ten minutes. The flow remains very slight for about two hours and then suddenly increases in amount during the third hour, corresponding thus very nearly to the flow of pancreatic juice excited by the same means. In this postprandial secretion of juice it is not probable that the nervous system takes any very large share, though its intervention in the secretion has not been excluded by direct experiment. There are certain facts which seem indeed to speak for an action of the central nervous system on the processes of intestinal secretion; not in the direction of augmentation, but in the direction of inhibition of secretion.

Thus it has been observed, on many occasions, that extirpation of the nerve plexuses of the abdomen or section of the splanchnic nerves causes a condition of diarrhœa, which may last for two or three days. This condition might be determined, either by an increased motor activity of the gut, or by removal of inhibitory impulses normally arriving at the intestinal glands. Such a view receives support from an experiment first performed by Moreau. The abdomen of a dog is opened under an anæsthetic, and three contiguous loops of small intestine are separated by means of ligatures from the rest of the gut. The middle loop is then denervated by destruction of all the nerve fibres lying on its blood vessels, as they course through the mesentery, care being taken not to injure the blood vessels themselves. The loops are then replaced in the abdomen and the animal left from four to sixteen hours. On killing the animal at the end of this time, it is often found that the middle loop, *i.e.*, the denervated loop, is distended with fluid having all the properties of ordinary intestinal juice, whereas the other two loops are empty. A series of comparative experiments by Mendel * and by Falloise † have shown that the secretion begins about four hours after the operation, increases for about twelve hours, and then rapidly declines, so that at the end of two days all three loops will be found empty. This has often been interpreted as due to the removal of inhibitory impulses passing from the central nervous system to the local secretory mechanism, and we have no direct evidence which can be adduced against such a view. It is possible, however, that the hyperæmia of the gut, which is produced by the processes of denervation, may be sufficient to account for the increased formation of intestinal juice, since the hyperæmia will tend to

* Mendel, Pflüger's Archiv., Vol. LXIII., p. 425, 1896.

† Falloise, Archives internat. de Physiol., Vol. I., p. 261, 1904.

pass off as the vessels recover a local tone, just as we have seen happens with the increased secretion.

It is not possible to explain the flow of intestinal juice, which follows a meal, by any assumption of nervous impulses transmitted through the local nerve plexuses of the gut, since these have been divided in the making of the fistula. If we exclude a nervous reflex action by the long paths, namely through the spinal cord and the sympathetic or vagus nerves, the flow which attends the passage of food into the first part of the duodenum must be excited by the formation of some chemical messenger. As to the existence of such a chemical messenger or hormone for the intestinal secretion, there can be no doubt, but the evidence as to its precise nature is at present conflicting. It is stated by Pawlow that the most effective stimulus to the flow of succus entericus is the presence of pancreatic juice in the loop of gut. In the few experiments which I have made on a fistula from the middle of the small intestine, I have not observed such a marked stimulating effect of pancreatic juice on intestinal secretion as is described by Pawlow, but it is possible that the effect of the local introduction of pancreatic juice may vary with the location of the fistula. No evidence has yet been brought forward that injection of pancreatic juice into the blood stream will cause any flow of intestinal juice. Whatever, therefore, may be the local effects of this juice, it is doubtful whether we can regard it as the hormone, whose absorption from the duodenum determines the postprandial flow of juice in the isolated loop of gut.

We have already seen that the simultaneous presence in the gut of the two juices, bile and pancreatic juice, whose co-operation is necessary for the full manifestation of the actions of each, is ensured by the presence of one and the same chemical messenger for the arousing of both secretions. Since

the co-operation of succus entericus is also necessary for the intestinal digestion, we might anticipate that the secretin, which excites both bile and pancreatic secretion, would also excite a secretion of succus entericus. That this is true, at any rate for the upper segments of the gut, has been shown by Délézenne and Frouin. In procuring pancreatic juice by the intravenous injection of secretin, it is always found that the small intestine contains a considerable quantity of fluid, presumably intestinal juice. This might be regarded as a secretion excited by the escape of a small amount of pancreatic juice into the gut along the second pancreatic duct, which is generally left unligatured in this experiment. The two French observers, however, have shown that in animals provided with a permanent fistula involving the duodenum or upper part of the jejunum, intravenous injection of secretin always causes a secretion of intestinal juice. In the upper part of the gut, therefore, the simultaneous presence of the three juices necessary for complete duodenal digestion is ensured by one and the same mechanism, namely, by the simultaneous activity of the secretin, produced in the intestinal cells by the action of the acid chyme, on pancreas, liver, and intestinal glands.

Recently a further chemical mechanism for the arousing of intestinal secretion has been described by Frouin. According to this observer, the flow of juice can be excited by intravenous injection of intestinal juice itself. Since this juice is alkaline, and does not produce any effect on the pancreas, it must be free from pancreatic secretin. It would seem, therefore, that the flow of juice in the upper part of the gut, excited by the pancreatic secretin, causes also a production of a different secretin or hormone, which can be absorbed from the lumen of the gut, travel by the blood stream to other segments of the small intestine, and there excite a secretion in preparation

for the oncoming food. Further experiments are, however, necessary on this point.

Besides this sensitiveness to chemical stimulation, the glands of the small intestine can be excited by direct mechanical stimulation of the mucous membrane. The easiest method of exciting a flow of intestinal juice from a permanent fistula is to introduce into the intestine a rubber tube. The presence of the solid object in the gut causes a secretion, and within a few minutes drops of juice can be obtained from the free end of the tube. The object of such a sensibility to mechanical stimuli is obvious; it is of the highest importance that the onward passage of any solid object, especially if it be indigestible, shall be aided by the further secretion of juice in the portions of gut which are immediately stimulated. This mechanical stimulation probably acts on the tubular glands of the intestine through the intermediation of the local nervous system, the plexus of Meissner. It is stated by Pawlow that a juice obtained by mechanical stimulation differs from that produced by the introduction of pancreatic juice into the loop, in containing little or no enterokinase. Apparently the pancreatic juice excites the secretion of the substance which is necessary for its own activation.

CHARACTERS OF INTESTINAL JUICE.

The intestinal juice obtained from a permanent fistula has a specific gravity of about 1010. It is generally turbid from the presence in it of migrated leucocytes and disintegrated epithelial cells. It contains about 1·5 per cent. total solids, of which ·8 per cent. are inorganic and consist chiefly of sodium carbonate and sodium chloride. It is markedly alkaline in reaction, but less so than the pancreatic juice. The organic matter, besides a small amount of serum albumen and serum globulin, includes a number of ferments, all of

which are adapted to complete the processes of digestion of the food-stuffs commenced in the stomach and duodenum. Of these ferments two are concerned in proteolysis. Enterokinase we have already studied in detail. Possessing no action itself on proteids, it is a necessary condition for the development of the full proteolytic powers of the pancreatic juice. In addition to this ferment another ferment has been described by Cohnheim under the name 'erepsin.' Erepsin or some similar ferment is present in the fresh pancreatic juice and in almost all tissues of the body. It is distinguished by the fact that, although it has no power of digesting coagulated proteid or gelatin, and only slowly dissolves caseinogen and fibrin, it has a rapid hydrolytic effect on the first products of proteolysis, converting albumoses and peptones into amino- and diamino-acids—their ultimate cleavage products.

The other ferments of the intestinal juice are all connected with the digestion of carbohydrates. In all mammals the intestinal juice is found to contain invertase, which transforms cane sugar into glucose and lævulose or fructose, and maltase which converts maltose into glucose. In young mammals, as well as in those in whom the milk diet is continued throughout life, the intestinal mucous membrane also contains lactase, *i.e.*, a ferment converting milk sugar into galactose and glucose. Such a ferment can be extracted from the mucous membrane of all young animals, but may be very slight or even absent in the intestines of older animals, when it is no longer needed for the ordinary processes of nutrition. By means of these three ferments, coming as they do after the digestion of the starches by the amylase of the saliva and pancreatic juice, it is provided that all the carbohydrate food of the animal is transformed into a hexose, in which form alone carbohydrate can be taken up and assimilated by the cells of

the body. If a disaccharide, such as cane sugar or lactose, be injected into the circulation, it is excreted unchanged in the urine. On the other hand the injection of moderate quantities of the hexoses, glucose, fructose, or galactose into the circulation does not lead to the appearance of the sugars in the urine, but causes an increased formation of glycogen by the liver. The seat of origin of these various ferments has been the subject of special investigation by Falloise.* Bayliss and I had already shown that secretin can be obtained from the whole thickness of the mucous membrane, and is probably therefore contained in the form of prosecretin in the epithelial cells covering the villi as well as in those lining the follicles of Lieberkuhn. On the other hand a superficial scraping of the mucous membrane, which removes only the epithelial cells covering the villi with the adherent mucus and intestinal secretion, gives a much more active solution of enterokinase than the deeper scraping of mucous membrane. This result is confirmed by Falloise, who therefore places the seat of production of enterokinase in the cells covering the intestinal villi. The most active solutions of enterokinase are, however, to be obtained from the fluid found in the cavity of the intestine after the injection of secretin. We are therefore inclined to believe that enterokinase is not present as such in the epithelial cells, but is first produced in the process of secretion and formation of the intestinal juice. The other ferments, namely erepsin, maltase, invertase, and lactase, probably pre-exist as such in the epithelial cells, especially in those lining the tubular glands of the gut, since pounded mucous membrane in water yields a solution of these ferments which is generally more powerful in its action than the succus entericus itself. So great is the difference, in fact, that many physiologists have suggested that the chief action of these

* Archives internat. de Physiol., Vol. II., p. 299, 1905.

ferments occurs, not in the lumen of the gut, but in the passage of the food-stuffs through the epithelial cells of the small intestine on their way to the blood vessels.

As the result of all these changes, the three classes of food-stuffs are reduced to a soluble condition, and in solution are taken up by the cells lining the intestine. In the case of the fats, the greater part are at once resynthesised into insoluble neutral fats in the cells themselves, and passed on in this form by the lacteals and lymphatic system into the blood stream. So far as experimental evidence goes, the sugars and disintegration products of the proteids pass directly into the blood stream, by which they are conveyed to the liver and other organs of the body, where they are either stored up or utilised in furnishing the energy required for the discharge of the bodily functions. Only to a small extent are they required for the building up of the tissues in replacement of loss by injury or local old age and death. The main function of the alimentary tract is, therefore, the presentation to the tissues of the body of the food-stuffs in a form in which they are directly assimilable.

LECTURE X.

THE MOVEMENTS OF THE ALIMENTARY TRACT.

An essential part in the digestive act is played by the continual movements, by means of which the food is intimately mixed with the digestive juices and gradually passed on from one segment of the canal to the next. By these movements the organism provides for: (1) the preparation of the food for digestion by reducing it to a condition of fine sub-division by means of the movements of mastication; (2) the intimate mixing of the food with the digestive juices, so as to allow of these coming in contact with every particle; (3) the propulsion of the food from one cavity of the canal to the next so soon as the processes of digestion in the first cavity have been completed; and (4) finally the rejection and expulsion from the body of the undigestible portions of the food-stuffs, mixed with the products of excretion of the wall of the alimentary canal itself.

Although the researches on the movements of the alimentary canal date from the very beginning of physiology, it is only within the last ten years that the enormous mass of facts and observations, which have been made, have been reduced to an orderly whole, so that we may form a conception of the course of events concerned in the movements of the food, from the time that it enters the mouth to the rejection of the undigested portions in the fæces. In the case of the secretory mechanism we have seen that, whereas the first parts of the alimentary canal are under the direct control of the central

nervous system, this control gets less and less with the onward progress of the food; and that, in the duodenum and small intestine, the mechanism for evoking the secretion of the digestive juices, at the exact time and place where they are required, is local or chemical, and occurs in the entire absence of any connection with the central nervous system. In the same way the motor reactions, which affect the beginning of the canal, are subject to the central nervous system. This direct control is also manifested in the reactions of the lowest portions of the gut, which are concerned in the act of defæcation. The middle of the alimentary canal however, although capable of being affected by the central nervous system through the splanchnic and vagus nerves, depends for the greater part of its activity on a nervous mechanism situated in the wall of the gut itself. The mechanism is apparently in all cases nervous, and we have, at present, no evidence of motor reactions being evoked by the circulation in the blood of chemical substances or hormones.* There must naturally be a wide variation in the details of the motor reactions of the alimentary canal, according to the nature of the food-stuffs chiefly made use of by the animal; and we find great differences in this respect, as in the anatomy of the canal, between a carnivorous animal such as the dog and a herbivorous animal such as the rabbit. In the following account I shall deal chiefly with those facts which, though determined by experiments on animals of both classes, can be directly applied to the movements of the alimentary tract in man.

After the food has been reduced by movements of the jaw,

* Apart, that is to say, from any co-operation on the part of nervous structures. Adrenalin, the hormone manufactured by the suprarenal bodies, seems to be necessary for the normal display of the functions of the sympathetic system, and its motor or inhibitory effects on the gut are produced through this system.

cheeks, and tongue to a state of fine pulp, it is collected by movements of the tongue into a bolus. This bolus is then rapidly thrust by movements of the tongue muscles back into the upper part of the œsophagus, its passage over the region of the pharynx common to the purposes of alimentation and respiration being effected rapidly, so as to interfere as little as possible with the respiratory movements. The œsophagus is a muscular tube lined internally with mucous membrane, which is constantly moistened with mucus secreted by numerous glands. The muscular coat consists of two layers, longitudinal fibres externally and circular fibres internally. In the upper part of the œsophagus both these layers are composed of voluntary striated muscle. In the lower third of the œsophagus the muscle is entirely of the unstriated variety, and in the middle part there is a gradual transition between these two types. The food, on arriving at the upper part of the tube, is passed rapidly down to the lower end and through the cardiac orifice into the stomach by means of a peristaltic contraction.

As this form of contraction plays a great part in the onward movement of food in all the tubular portions of the alimentary canal, it may be well to define here more explicitly what we mean by the term 'peristalsis.' A peristaltic contraction is a co-ordinated act, comparable in many respects with the co-ordinated movement of extension or flexion which occurs in a limb as a result of an appropriate sensory stimulus. Each such co-ordinated movement involves, as has been so ably demonstrated by Sherrington, two opposed processes—excitation and inhibition. If, for instance, the leg be flexed in response to a painful stimulus applied to the sole of the foot, this flexion includes contraction of the flexor muscles and inhibition of the extensor muscles. If the flexor muscles be divided, it is still possible to show that the extensor muscles undergo

a lengthening as the result of the application of the stimulus. In the same way a movement of extension of the leg, in response to a particular tactile stimulus applied to the ball of the foot, can be properly carried out only by a two-fold discharge causing inhibition of the flexor muscles, and contraction of the extensor muscles. The uncoordinated spasms which distinguish strychnine poisoning are due to the abolition of the inhibitory part of each reflex and its conversion into a contractile reaction, so that antagonistic muscles are set into contraction by one and the same sensory stimulus. The physiological purpose of a peristaltic contraction is the propulsion of a solid or semi-solid object along a tube. A simple contraction of the tube, even if propagated along its walls, would probably pass over the object, squeezing it in its course but not effecting an onward movement. In order that the object or bolus may be moved from one end of the tube to the other, it is necessary that a process of contraction of the muscle behind it should be accompanied with a process of relaxation of the muscular walls of the tube in front of it. This is the distinguishing feature of a peristaltic contraction—a process of contraction behind the object, and a process of inhibition and relaxation in front of the object. Such a double process can be effected only by a co-ordinating centre. In the case of the œsophagus this co-ordinating centre is situated in the medulla, and the orderly progression of the peristaltic wave of inhibition *plus* contraction along the walls of the tube is dependent on the integrity of the branches of the vagus nerve, by which the medullary centre is united to the gullet. Division of these nerves destroys the power of swallowing. If food be thrust by the movements of the tongue into the upper part of the œsophagus, this latter may become filled up with food. The food cannot pass into the stomach on account of the absence of the one definite factor in the peristaltic

contraction, namely the inhibition in front of the bolus, an inhibition which involves also the cardiac sphincter of the stomach. It seems that, under normal conditions, a stimulus applied to the root of the tongue or back of the pharynx and travelling by the superior laryngeal nerves to the vagus centre in the medulla, causes a fusillade discharge from the centre along the successive fibres of the vagus, an inhibitory discharge preceding in each case the motor discharge.

In man the peristaltic wave takes about five to six seconds to pass from the level of the glottis to the stomach, the passage being rapid in the upper third, in the region of the striated muscle, and gradually becoming slower as the striated muscle gives place to involuntary muscle. When a series of swallowing movements are carried out, the lower end of the œsophagus remains in a state of inhibition, and we have simply a series of annular constrictions passing down the œsophagus behind each food bolus. The arrival of each bolus in the stomach can be detected by auscultating the back of a patient over the region of the cardiac orifice. A gurgling sound is heard each time the food passes into the stomach.

MOVEMENTS OF THE STOMACH.

When a meal is taken the inhibition, which precedes the passage of each bolus, spreads to the whole stomach wall, so that any movements, which have been present before the meal, come to an end, and the stomach is in a relaxed and passive condition ready to receive the food passing to it from the mouth. The food passes into the large fundus of the stomach and accumulates there to form one mass. The stomach remains passive for some time after the beginning of a meal, and it is not until twenty to thirty minutes later that the first movements make their appearance. Secretion of gastric juice commences even while the food is in the mouth.

The acid juice cannot, however, penetrate the great mass of food which is lying in the fundus, and in the interior of this mass salivary digestion can go on from thirty minutes to one and a half hours after the food has been swallowed. A very considerable portion therefore of the salivary digestion occurs in the stomach itself. For the understanding of the subsequent movements of the gastric wall, it is important to remember its functional division into two parts, namely, fundus and pyloric end or antrum. Although the dead stomach appears to form one sac, observation of a stomach, recently removed from the living animal and placed in warm salt solution, shows distinctly this division into two parts, namely, a tubular part at the pyloric end and a bag-like portion, forming four-fifths of the stomach, at the cardiac end. The division between the two is marked by what has been called the 'transverse band' of the stomach, a region where there is almost always contraction of the circular muscle fibres. So marked is this in the living stomach that one would expect on dissection to find evidence of sphincter-like thickenings at this point. It is, however, a physiological and not an anatomical condition.

The movements of the stomach can be best studied by Cannon's method, that is, by direct observation of the movements in a living unanæsthetised animal, by means of the Röntgen rays. In order to make the shape of the stomach visible, the food—bread and milk—is mixed with a quantity of bismuth subnitrate. The presence of this salt does not interfere with the processes of digestion, but renders the gastric contents opaque to the Röntgen rays. On examining by this means the stomach of a cat, which has just taken a meal, the whole of the food is seen to be lying in the fundus. It is marked off by a strong constriction of the transverse band from the antrum. In about twenty to thirty minutes,

faint waves of contraction begin a little to the cardiac side of the transverse band and travel slowly towards the pylorus. These waves succeed one another, so that the pyloric part of the stomach may present a series of constrictions. The effect of these waves is to force the food, which has been digested by the gastric juice and detached from the surface of the mass of food in the fundus, towards the pylorus. The pylorus remaining closed, the food cannot escape, and therefore is squeezed back, forming an axial reflux stream towards the cardiac end. These contractions last throughout the whole period of gastric digestion and become more marked as digestion proceeds. Their effect is to bring the whole of the food in close contact with every particle of pyloric mucous membrane, and to cause a thorough mixture of food and gastric juice. At varying periods after a meal, according to the nature of the food taken, the arrival of one of these waves of contraction at the pylorus causes a relaxation of its orifice, and a few cubic centimetres of gastric contents are squirted into the first part of the duodenum. While these movements of the pyloric mill are going on, the cardiac portion of the stomach is exercising a steady pressure on its contents, in consequence of a tonic contraction of its muscular wall, so that each successive portion of the food mass, which is loosened by the digestive action of the gastric juice, is forced on into the pyloric mill. As digestion proceeds, the opening of the pylorus becomes more frequent. The stomach empties itself more and more, until finally the whole of the viscus has the shape of a curved tube. At the very end of digestion, the pylorus may open to allow the passage even of undigested morsels of food.

These movements of the two portions of the stomach may be observed also on anæsthetised animals, and even on a stomach which has been excised and placed in warm salt

solution. They must therefore have their origin in the walls of the stomach itself. Although the co-ordination between the two parts of the stomach, between the tonic contraction of the fundus and the rhythmic contractions of the antrum, may be carried out by the local nervous system—Auerbach's plexus—situated between the layers of the muscular coat, it is probable that the advancing waves of contraction observed in the antrum are myogenic, *i.e.*, directly originated in and determined by the muscle fibres themselves. Although we have no direct evidence that these movements persist after throwing the local nervous system out of action, it is evident that they do not partake of the nature of a true peristalsis, since they are not preceded by a wave of relaxation. The opening of the pylorus, on the other hand, which occurs at increasingly frequent intervals at the end of a wave, must be ascribed to a nervous mechanism. The local mechanism probably plays the greater part in this act of relaxation, though there is no doubt that the normal emptying of the stomach is also largely dependent on the integrity of the connection of this viscus with the central nervous system. If both vagus nerves be divided in a dog, below the point at which they give off their branches to the lungs and heart, it is found that a large amount of food remains in the stomach in an undigested condition. The secretion of gastric juice is deficient, the movements of the stomach are also deficient, and the opening of the pylorus is not easily carried out. Such dogs, therefore, tend to die of sapræmia, being poisoned by the absorption of products of putrefaction from the gastric contents. Pawlow has shown that animals can be kept alive for months after division of both vagi, if a gastric fistula be made, the animals be carefully fed, and care be taken to wash out adherent non-digested portions of food from the stomach.

The opening of the pylorus depends not only on intragastric

events but also on the condition of the duodenum. It has been shown by Serdjukow* that the pylorus remains firmly closed so long as the contents of the duodenum are acid. If alkaline fluid be introduced into the stomach, this is rapidly passed into the duodenum. If, however, some acid be introduced at the same time into the duodenum by means of a duodenal fistula, the pylorus remains firmly closed, and no fluid passes into the duodenum until the acid, which was placed there, has been neutralised by the secretion of pancreatic juice and succus entericus. We have therefore, in the walls of the alimentary canal, a local nervous mechanism for the movements of the pyloric sphincter. This may be played upon by impulses starting either in the stomach or in the duodenum, probably by the contact of acid with the mucous membrane. Increasing acidity on the side of the stomach causes relaxation of the orifice, whereas acidity on the duodenal side causes contraction of the pyloric sphincter. The exact parts played in this mechanism by the local system and by the central nervous system respectively have not yet been thoroughly made out.

MOVEMENTS OF THE INTESTINES.

The movements of the intestines can be investigated either by observation of the exposed gut, or by the shadow method introduced by Cannon, in which the nature of the movements is judged from the shadows of food containing bismuth which are thrown on a sensitive screen by means of the Röntgen rays. These movements have been the subject of experimental investigation for many years, but with very varying results. The great discrepancy, which obtained between the statements of earlier observers, is due to the fact that they failed to exclude

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* Quoted by Pawlow, *loc. cit.*, p. 164.

the many disturbing impulses which can play on any segment of the gut, either reflexly through the central nervous system, or from other parts of the alimentary canal itself through the local nervous system. In order to observe the normal movements of the gut, it is necessary to exclude the disturbing influences due to reflexes through the central nervous system, either by extirpation of the whole of the nerve plexuses in the abdomen, or by division of the splanchnic nerves, or by destruction of the lower part of the spinal cord from about the middle dorsal region. If the abdomen of an animal, which has been treated in this way, be opened in a bath of warm normal salt solution, so as to exclude the disturbing influence of drying and cooling of the gut, the small intestine will be seen to present two kinds of movements. In the first place, all the coils of gut undergo swaying movements from side to side—the so-called pendular movements. Careful observation of any coil will show that these movements are attended with slight waves of contraction passing rapidly over the surface. If a rubber balloon, filled with air and connected with a tambour, be inserted into any part of the gut, it will show the existence of rhythmic contractions of the circular muscle repeated from twelve to thirteen times per minute. By means of a special piece of apparatus (the 'enterograph'), it is possible without opening the gut to record the movements of either circular or longitudinal muscular coats; and it is then found that both coats present rhythmic contractions at the same rate, the two coats at any point contracting synchronously. When the contractions are recorded by means of a balloon, the constriction which accompanies each contraction is seen to be most marked at the middle of the balloon, *i.e.*, at the point of greatest tension, and the amplitude of the contractions is augmented by increasing the tension on the walls of the gut. These movements are unaffected by the direct

application of drugs such as nicotine or cocaine, which we might expect to paralyse any local nervous structures in the wall of the gut. Bayliss and I therefore concluded that these rhythmic contractions were myogenic,* that they were propagated from muscle fibre to muscle fibre, and that they coursed down the gut at the rate of about 5 cm. per second. Since, however, they may apparently arise at any portion of the gut which is subject to any special tension, it is not easy to be certain that a contraction recorded at any point is really propagated from a point two or three inches higher up. We suggested that the action of these contractions was to cause a thorough mixing of the contents of the gut with the digestive fluids.

The exact value of these movements for the digestive processes is shown very clearly when they are observed by Cannon's method.† On examining under the Röntgen rays the intestines of a cat, which has taken a large meal of bread and milk mixed with bismuth some hours previously, a length of gut may be seen, in which the food contents form a continuous column. Suddenly movements occur in this column, which is split into a number of equal segments. Within a few seconds each of these segments is halved, the corresponding halves of adjacent segments uniting. Again contractions

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* Magnus has shown that it is possible to pull off strips of the longitudinal (outer) coat of muscle fibres from the small intestine. Such strips, if they contain Auerbach's plexus, will contract rhythmically if kept in warm oxygenated Ringer's fluid. If, however, the plexus has been left behind in stripping off the muscle, no rhythmic contractions are to be observed, although contraction can still be excited by artificial stimulation. Magnus concludes that even the rhythmic 'pendular' contractions depend for their occurrence on the integrity of the connection between local ganglionic centres and muscle fibres, and cannot therefore be strictly regarded as myogenic (*Pflüger's Archiv.*, CII., p. 349, 1904).

† Cannon. *Amer. Journ. of Physiol.*, Vol. VI. p. 251, 1901.

recur in the original positions, dividing the newly-formed segments of contents and re-forming the segments in the same position as they had at first (Fig. 12). If the contraction is a continuous propagated wave, it is evidently reinforced at regular intervals down the gut, so as to divide the column of food into a number of spherical or oval segments. In this way the points of greatest tension immediately become the points which are midway between the spots where the

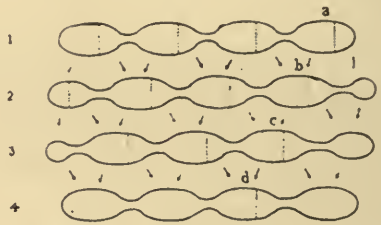

FIG. 12. Diagram (from Cannon) showing the appearance of a length of gut filled with food contents. Each of the portions, into which the contents are divided, are segmented by subsequent contractions at two points (shown by dotted lines) and then return to their first condition. The arrows indicate the relation of the pieces to the portions they subsequently form.

first contractions were most pronounced. The second contractions, therefore, start at these points of greatest tension, and divide the first formed segments into two parts, which join with the corresponding halves of the neighbouring segments. In this way every particle of food is brought successively into intimate contact with the intestinal wall. These movements have not a translatory effect, and a column of food divided up in this way may remain at the same level in the gut for a considerable time.

The onward progress of the food is caused by a true peristaltic contraction, *i.e.*, one which involves contraction of the

gut above the food mass and relaxation of the gut below. If a balloon be inserted in the lumen of the exposed gut, it will be found that pinching the gut *above* the balloon causes an immediate relaxation of the muscular wall in the neighbourhood of the balloon. This inhibitory influence of the local stimulus may extend as much as two feet down the intestine towards the ileo-cæcal valve. On the other hand, pinching

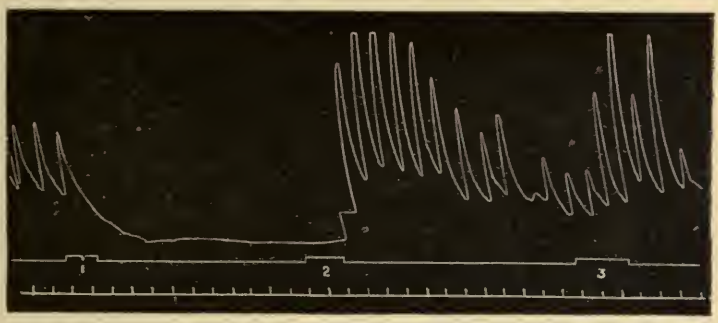

FIG. 13. Rhythmic contractions of the wall of the small intestine (dog) recorded by inserting a rubber balloon into the lumen of the gut, and connecting it by a tube with a piston recorder. At the signal (1), the intestine was gently pinched one inch *above* the balloon. The effect was immediate and lasting inhibition. At (2) and (3) the intestine was pinched half an inch *below* the balloon with the result of causing in each case increased contractions at the level of the balloon. (Bayliss and Starling.)

the gut half an inch below the situation of the balloon causes a strong continued contraction to occur at the balloon itself (Fig. 13). We see, therefore, that stimulation at any portion of the gut causes contraction above the point of stimulus and relaxation below the point of stimulus (the 'law of the intestines'). The same effect is produced by introduction of a bolus of food, especially if it be large or have a direct irritating effect on the wall of the gut. In this case the contraction above and the inhibition below cause an onward movement

of the bolus, which travels slowly down the whole length of the gut until it passes through the ileo-cæcal opening into the large intestine. The peristaltic contraction involves, as I have mentioned before, the co-operation of a nervous system. Whereas in the œsophagus it was the central nervous system which was involved, the peristaltic contractions in the small intestine occur after severance of all connection with the brain and spinal cord. On the other hand, it is absolutely abolished by painting the intestine with nicotine or with cocaine. It must therefore be ascribed to the local nervous system contained in Auerbach's plexus, which we can regard as a lowly organised nervous system with practically one reaction, namely, that which we have formulated above as the 'law of the intestines.' An anti-peristalsis is never observed in the small intestine. Mall * has shown that, if a short length of gut be cut out and re-inserted in the opposite direction, a species of partial obstruction results, in consequence of the fact that the peristaltic waves, started above the point of operation, cannot travel downwards over the reversed length of gut. The intestine above this point therefore becomes dilated. If, however, the reactions of the local nervous system be paralysed or inhibited, a reflux of intestinal contents is quite possible, since the contractions excited at any spot by local stimulation of the muscle have the effect of driving the food either upwards or downwards; the direction of movement of the food will be that of least resistance.

The movements of the small intestine are also subject to the central nervous system. Stimulation of the vagus has the effect of producing an initial inhibition of the whole small intestine, followed by increased irritability and increased contractions. On the other hand, stimulation of the splanchnic

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* *Johns Hopkins Hospital Reports*, Vol. I. p. 37, 1896.

nerves causes complete relaxation of both coats of the small gut. It seems that the splanchnics normally exercise a tonic inhibitory influence on the intestinal movements, which can be increased by all manner of peripheral stimuli. On this account it is often impossible to obtain any movements in the exposed intestine, so long as these remain in connection with the central nervous system through the splanchnic nerves. The relaxed condition of the gut, which obtains in many abdominal affections, is probably also reflex in origin, and is due to reflex inhibition through the splanchnic nerves.

As a result of the two sets of movements described above, the food is thoroughly mixed with the digestive juices, and the greater part of the products of digestion are brought into contact with the intestinal wall and absorbed. What is left—a proportion varying in different animals according to the nature of the food—is passed on by occasional peristaltic contractions through the lower end of the ileum into the colon, or large intestine. The lowest two centimetres of the ileum present a distinct thickening of its circular muscular coat forming the ileo-colic sphincter. This sphincter relaxes in front of a peristaltic wave and so allows the passage of food into the colon. On the other hand, it contracts as a rule against any regurgitation which might be caused by contractions in the colon. Although thus falling into line with the rest of the muscular coat, as concerns its reaction to stimuli arising in the gut above or below, it presents a marked contrast to the rest of the gut in its relation to the central nervous system. It is apparently unaffected by stimulation of the vagus. Stimulation of the splanchnic however, which causes complete relaxation of the lower part of the ileum with the rest of the small intestine, produces a strong contraction of the muscle fibres forming the ileo-colic sphincter.

MOVEMENTS OF THE LARGE INTESTINE.

By means of the occasional peristaltic contractions, accompanied by relaxation of the ileo-colic sphincter, the contents of the small intestine are gradually transferred into the large.

In man, these contents are considerable in bulk, are semi-fluid, and probably fill the ascending as well as the transverse colon.

The large intestine is supplied with nerves from the central nervous system. These run partly in the sympathetic system along the colonic and inferior mesenteric nerves, partly in the pelvic visceral nerves or *nervi erigentes*, which come off from the sacral cord and pass direct to the pelvic viscera. In addition it possesses a local nervous system, presenting the same structure as that found in the small intestine. The movements of the large intestine differ considerably in various animals, as has been shown by Elliott, according to the nature of the food and the part played by this portion of the gut in the processes of absorption. In the dog the process of absorption is almost complete at the ileo-colic valve, whereas in the herbivora a very large part of the processes of digestion and absorption occurs in the colon and cæcum. Man takes an intermediate position as regards his large intestine between these two groups of animals. Bayliss and I, working on dogs, were able to demonstrate a local reaction in the large gut similar to that we had described in the small. Elliott* has shown however that, if one considers a number of different animals, one must divide the large intestine into four parts, according to their functions, viz., the cæcum, and the proximal, intermediate and distal portions of the colon. Of these the

* Elliott and Barclay-Smith, *Journ. of Physiol.* Vol. XXXI. p. 272, 1904.

dog possesses practically only the distal colon. We may take Elliott's account of the movements as they probably occur in man. They agree very closely with those observed by Cannon under normal circumstances in the cat, by means of the Röntgen rays. The food as it passes from the ileum first fills up the proximal colon. The effect of this distension is to cause a contraction of the muscular wall at the junction between the ascending and transverse colon. This contraction travels slowly over the tube in a backward direction towards the cæcum, and is quickly succeeded by another, so that the colon may present at the same time several of these advancing waves. These waves are spoken of as anti-peristaltic; but, as they do not involve also an advancing wave of inhibition, they must not be regarded as representing the exact antithesis of a peristaltic wave, as we have defined it. The effect of these waves is to force the food up into the cæcum, regurgitation into the ileum being prevented partly by the obliquity of the opening, partly by the tonic contraction of the ileo-colic sphincter. As the whole of the contents cannot escape into the cæcum, a certain portion will slip back in the axis of the tube, so that these movements have the same effect as the similar contractions in the pyloric end of the stomach, causing a thorough churning up of the contents and its close contact with the intestinal wall. The movements are rendered still more effective by the sacculation of the walls of this part of the large intestine. The distension of the cæcum caused by this anti-peristalsis excites occasionally a true co-ordinated peristaltic wave, which, starting in the cæcum, drives the food down the intestine into the transverse part. These waves die away before they reach the end of the colon, and the food is driven back again by waves of anti-peristalsis. Occasionally more food escapes through the ileo-colic sphincter from the ileum, so that the whole ascending and transverse colon

may be filled with the mass undergoing a constant kneading and mixing process. The result of this process is the absorption of the greater part of the water of the intestinal contents, as well as of any nutrient material, and the drier part of the intestinal mass collects towards the splenic flexure, where it may be separated by transverse waves of constriction from the more fluid parts which are being driven to and fro in the proximal and intermediate portions. By means of occasional peristaltic waves these hard masses are driven into the distal part of the colon. The distal colon must be regarded as a place for the storage of the fæces, and as the organ of defæcation. In the transverse colon, in the descending and ileo-colon, the anti-peristaltic movements and consequent churning of the contents are probably slight. These therefore represent the intermediate colon with propulsive peristalsis as its chief activity. The descending colon is never distended, and Elliott therefore regarded it as a transferring segment of exaggerated irritability. The storage of the waste matter takes place chiefly in the sigmoid flexure. This with the rectum represents the distal portion of the colon. The distinguishing feature of the distal colon is its complete subordination to the spinal centres. It probably remains inactive until an increasing distension excites reflexly through the pelvic visceral nerves a complete evacuation of this portion of the gut. Stimulation of these nerves in an animal, such as the cat, produces a rapid shortening of the distal part of the colon, due to contraction of the recto-coccygeus and longitudinal fibres of the gut, followed after some seconds by a contraction of the circular coat. This originates at the lower limit of the area of anti-peristalsis, *i.e.*, probably at the upper end of the sigmoid flexure, and spreading rapidly downwards, empties the whole of this segment of the gut. In man the emptying of the rectum itself is, of course, largely assisted

by the contractions of the voluntary muscles of the abdominal walls and pelvic floor.

We see, then, that the whole of the movements of the alimentary canal are completely adapted to effect the digestion and absorption of the food-stuffs. At the upper and lower ends of the canal, these movements are under the direct control of the central nervous system, since they have to be guided in accordance with the requirements of the animal's environment. In the middle parts of the gut, where the processes of digestion and absorption must go on without reference to the external conditions or activities of the animal, the movements are chiefly determined by local mechanisms. Even here, however, they can be completely abolished, through the spinal cord and sympathetic system, in cases where injury of the abdominal cavity may render the local activities dangerous for the animal. The complete paralysis of the gut, which has been observed in cases of gun-shot wound of the abdomen, is probably protective in function and determined by splanchnic stimulation.

The motor activities of the alimentary canal present an ordered march of events as suited to the needs of the organism as are those which we have studied in dealing with the secretion of the digestive fluids. They differ from these in being more rapidly adaptable, and are therefore determined entirely by nervous mechanisms. So far as we know, chemical mechanisms play no part in the muscular activities of any part of the alimentary canal.

APPENDIX.

LIST OF PAPERS,

Bearing on the Subjects treated of in the preceding Lectures, which have been published since 1899 by Workers in the Physiological Department, University College.

LECTURE I.

(1) "Some Researches on the Autolytic Degradation of Tissues." Pt. I. By Janet E. Lane-Claypon, B.Sc., and S. B. Schryver, D.Sc. (*Journ. of Physiol.*, Vol. XXXI., 1904.)

(2) "Researches on the Autolytic Degradation of Tissues." By S. B. Schryver. Pt. II. (*Journ. of Physiol.*, Vol. XXXII., 1905.)

LECTURE II.

(3) "The Kinetics of Tryptic Action." By W. M. Bayliss, F.R.S. (*Archives des Sciences Biol.*, Vol. XI., Suplt. St. Petersburg, 1904.)

(4) "The Effect of Electrolytes on Adsorption." By W. M. Bayliss. (*Biochemical Journal*, Vol. I., 1906.)

(5) "The Separation of Phosphorus from Caseinogen by the Action of Enzymes and Alkali." By R. H. Aders Plimmer, D.Sc., and W. M. Bayliss, F.R.S. (*Journ. of Physiol.*, Vol. XXXIII., p. 439, 1906.)

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LECTURE III.

(6) "On the Changes in Volume of the Submaxillary Gland during Activity." By J. Le M. Bunch, D.Sc., M.D. (*Journ. of Physiol.*, Vol. XXVI., 1900.)

(7) "Observations on the Lymph Flow from the Submaxillary Gland of the Dog." By F. A. Bainbridge, B.A., B.Sc. (*Journ. of Physiol.*, Vol. XXVI., 1900.)

LECTURE V.

(8) "On the Causation of the so-called 'Peripheral Reflex Secretion' of the Pancreas." (Preliminary communication.) By W. M. Bayliss and E. H. Starling. (*Proc. Roy. Soc.*, January 23, 1902.)

(9) "The Mechanism of Pancreatic Secretion." By W. M. Bayliss and E. H. Starling. (*Journ. of Physiol.*, Vol. XXVIII., 1902.)

(10) "On the Uniformity of the Pancreatic Mechanism in Vertebrata." By W. M. Bayliss and E. H. Starling. (*Journ. of Physiol.*, Vol. XXIX., 1903.)

(11) "On some Pathological Aspects of Recent Work on the Pancreas." By E. H. Starling. (*Trans. of Path. Soc. of London*, Vol. LIV., 1903.)

(12) Croonian Lecture (Royal Society) on "The Chemical Regulation of the Secretory Process." By W. M. Bayliss and E. H. Starling. (*Proc. Roy. Soc.*, Vol. LXXIII., 1904.)

LECTURE VI.

(13) "The 'Islets of Langerhans' in the Pancreas." By H. H. Dale, B.Ch. (*Proc. Roy. Soc.*, Vol. LXXIII., 1904, and *Phil. Trans. Roy. Soc.*, Series B, Vol. CXCVII., 1904.)

(14) "The Oxygen Exchange of the Pancreas." By J. Barcroft and E. H. Starling. (*Journ. of Physiol.*, Vol. XXXI., 1904.)

(15) "The Lymph Flow from the Pancreas." By F. A. Bainbridge, M.D. (*Journ. of Physiol.*, Vol. XXXII., 1904.)

LECTURE VII.

(16) "On the Composition of the Pancreatic Juice." By L. A. E. de Zilwa, M.B. (*Journ. of Physiol.*, Vol. XXXI., 1904.)

(17) "The Proteolytic Activities of the Pancreatic Juice." By W. M. Bayliss and E. H. Starling. (*Journ. of Physiol.*, Vol. XXX., 1903.)

(18) "On the Relation of Enterokinase to Trypsin." By W. M. Bayliss and E. H. Starling. (*Journ. of Physiol.*, Vol. XXXII., 1905.)

(19) "On the Adaptation of the Pancreas to Different Food-stuffs." (Preliminary communication.) By F. A. Bainbridge. (*Proc. Roy. Soc.*, Vol. LXXII., 1903.)

(20) "On the Adaptation of the Pancreas." By F. A. Bainbridge. (*Journ. of Physiol.*, Vol. XXXI., 1904.)

(21) "On the Alleged Adaptation of the Pancreas to Lactose." By R. H. Aders Plimmer, D.Sc. (*Journ. of Physiol.*, Vol. XXXIV., 1906.)

(22) "On the Identity of Trypsinogen and Enterokinase respectively in Vertebrates." By J. Molyneux Hamill, M.A., M.B. (*Journ. of Physiol.*, Vol. XXXIII., 1906.)

(23) "On the Mechanism of Protection of Intestinal Worms, and its Bearing on the Relation of Enterokinase to Trypsin." By J. M. Hamill. (*Journ. of Physiol.*, Vol. XXXIII., 1906.)

LECTURE VIII.

(24) For "Action of Secretin on Bile" *v.* Paper No. (9) in *Journ. of Physiol.*, Vol. XXVIII., 1902.

(25) "The Contractile Mechanism of the Gall Bladder and its Extrinsic Nervous Control." By F. A. Bainbridge and H. H. Dale. (*Journ. of Physiol.*, Vol. XXXIII., 1905.)

(26) "A Note on Hüfner's Method of Preparing Pure Glycocholic Acid." By W. A. Osborne. (*Proc. Physiol. Soc.*, 1900.)

(27) "On the Formation of Lymph by the Liver." By F. A. Bainbridge. (*Journ. of Physiol.*, Vol. XXVIII., 1902.)

LECTURE IX.

(28) "The Presence of Lactose in Animals." By R. H. Aders Plimmer. (*Proc. Physiol. Soc.*, 1906.)

(29) Croonian Lectures given at the Royal College of Physicians, London, "On the Chemical Correlation of the Functions of the Body." By E. H. Starling. (Published in *Lancet*, August, 1905.)

LECTURE X.

(30) "The Movements and Innervation of the Small Intestine." Pt. I. By W. M. Bayliss and E. H. Starling. (*Journ. of Physiol.*, Vol. XXIV., 1899.)

(31) *Idem.* Pts. II. and III. (*Journ. of Physiol.*, Vol. XXVI., 1901.)

(32) "The Movements and Innervation of the Large Intestine." By W. M. Bayliss and E. H. Starling. (*Journ. of Physiol.*, Vol. XXVI., 1901.)

(33) "On the Movements and Innervation of the Stomach." By W. Page May, M.D. (*Brit. Med. Journ.*, Sept. 13, 1902.)

(34) "The Innervation of the Sphincters and Musculature of the Stomach." By W. Page May. (*Journ. of Physiol.*, Vol. XXXI., 1904.)

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